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MUMPS ENCEPHALITIS

PATHOLOGY AND PATHOGENESIS

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ALTHOUGH clinical involvement of the nervous system in mumps is common, complete and uneventful recovery is the rule. Reports in the literature of mumps encephalitis which has terminated fatally are few and even rarer are accounts in which a histologic study of the nervous system has been made in those cases which came to post mortem.

In 1941 one of us (W.L.D.)[1] reported a fatal case of mumps encephalitis and made a review of the literature up to that time. In 1954 there was an opportunity to study a second fatal case. Because of the scarcity of such material and the conflicting descriptions of the lesions encountered in the few cases reported both prior to and after the above review, it was considered that both of the cases studied personally should be reported together. The lesions in our two cases are in all essentials identical and similar to those described in the few unequivocal cases reported in the literature. The characteristic lesion in the central nervous system is an acute perivascular demyelinization similar to that seen in the other postinfectious encephalitides.

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Because of the great advances that have been made recently in our knowledge of mumps virus infections, some indirect evidence may be adduced as to the pathogenesis of the postinfection encephalitides.

Clinical involvement of the nervous system in mumps is not rare and may be manifested in a variety of ways. The most familiar is the so-called meningitis or meningo-encephalitis which is characterized by an increase of cellular elements, chiefly lymphocytes, in the cerebrospinal fluid. This pleocytosis of the cerebrospinal fluid may or may not be accompanied by symptoms and signs of encephalitis or meningeal irritation. Latent encephalitis of mumps is an unusual phenomenon in which there may be a slight or pronounced increase of cells in the cerebrospinal fluid without symptoms or overt signs to indicate nervous system involvement. In addition, a significant number of the cases of so-called "acute aseptic meningitis" in which there is no clinical evidence of parotid, testicular, or visceral involvement will be due to mumps virus.[2, 3] These may be confused with nonparalytic poliomyelitis.

Other less common neurological manifestations which have been de-

scribed are myelitis, polyneuritis, and neuritis limited to one or more nerves such as the facial, trigeminal, auditory, and optic. Although some of these may result in permanent damage, more frequently the paresis or paralysis is transient and complete recovery occurs.[4]

It has been estimated that from less than 1 per cent to approximately 35 per cent of patients infected with mumps virus will show clinical or laboratory evidence of meningo-encephalitis.[3, 5, 6] None of these figures probably represent a true incidence, as most observations are made in military institutions and give only the adult male incidence during an epidemic. Since mumps is largely a benign disease of childhood, treated at home, those cases which enter hospital are unusually severe or have developed complications; hence, hospital statistics will be misleading and no data exist that will include all the home cases. Unless special diagnostic procedures such as the complement fixation tests are employed, cases of so-called aseptic meningitis due to mumps virus will be completely missed. As a rule, the more complete and painstaking the investigation in regard to possible neurological involvement in mumps infection, the more frequently this complication will be detected.

In 1937 de Lavergne and associates[7] reviewed the literature concerning mumps encephalitis and found only twelve patients with mumps who had died as a result of neurological complication. In only four of these had a microscopic examination of the nervous system been made. Another review was made in 1947 by Eberlein and Lynxwiler.[8] From these reviews and from additional reports in the readily available literature dating from 1900, which stated that they concerned fatal cases of mumps encephalitis, a total of only twenty cases has been found in which the neuropathological changes have been even briefly described.

CASE REPORTS

CASE 1.—The following patient was admitted to The Hospital for Sick Children, Toronto, Sept. 7, 1940, and died three days later; the case has been previously reported.[1]

J. K., a 5-year-old white girl, had snuffles and a dry cough for three days prior to the development of a left parotid swelling. Two days later the right parotid was similarly affected. Five days after the onset of the original parotid swelling and three days prior to admission, both parotid swellings had almost completely subsided. The child had been up and around with nothing unusual noted by the parents until approximately thirty hours prior to admission, when she appeared to be unable to see where she was going. A short time later she had several severe chills and seemed stuporous and dazed. Weakness of the legs developed. The night previous to admission she wakened repeatedly screaming.

On admission, the child was dazed, irrational, and obviously acutely ill. Temperature was 102° F; pulse 120; respirations 28. Aside from the nervous system, the physical examination was essentially negative. The cranial nerves appeared to be normal except for a right internal strabismus. The extremities were slightly hypertonic. Voluntary power was untestable but involuntary resistance to movement was considerable. She reacted to pinprick over the entire body. Reflexes were normal but hyperactive. Kernig's and Babinski's signs were present. The cerebrospinal fluid was under slightly increased pressure, clear, and contained 45 cells per cubic millimeter, of which approximately 90 per cent were lymphocytes. It was sterile on culture. Blood Wassermann and tuberculin

tests were negative. Although she remained unconscious, there seemed to be some slight improvement in the first twenty-four hours. However, she subsequently deteriorated rapidly and died three days after admission with evidence of pulmonary complications.

Autopsy Report.—The post-mortem examination was performed two hours after death. Only the positive findings will be mentioned. There was a patchy consolidation of both lungs. Both parotid and submaxillary glands appeared grossly normal and were not enlarged or congested although there were a few enlarged and firm lymph glands in their immediate neighborhood. The brain and cord showed a diffuse pinkish blush and a moderate congestion of the superficial vessels. There was no gross evidence of exudate. After fixation in Formalin, the cut surface of the brain and various levels of the cord showed a slight congestion of the blood vessels. Around some of the vessels in the white matter of the cerebrum and cerebellum there was a narrow, ill-defined, pale yellowish discoloration.

Microscopic Examination.—Lungs: There were patchy and confluent areas of typical bronchopneumonia. *Pancreas:* Normal. *Ovary:* The tissue was congested, and there were several small follicular cysts. In one of these there was a scanty exudate of mononuclears and polymorphs. This might possibly be interpreted as a mild oophoritis. There was, however, no inflammatory infiltration in the stroma. *Parotid and submaxillary glands:* Both these tissues presented essentially the same changes. These were somewhat more marked in the parotid than in the submaxillary. There was an extensive interstitial infiltration with lymphocytes and mononuclears (Figs. 1 and 2). This was most marked about the ducts, many of which were distended with plugs of inspissated secretion and contained, in addition, a few polymorphs. The epithelium lining the ducts, although somewhat flattened, was intact. The infiltration had resulted in some compression of the acinous tissue, but this tissue did not appear to be extensively involved. Inclusion bodies were not seen. *Brain and cord:* There was a slight diffuse infiltration of the meninges of the brain and cord with lymphocytes and a few mononuclears. The vessels were moderately congested. The characteristic lesion throughout the parenchyma of the central nervous system was essentially a perivascular demyelinization with attendant reaction on the part of the glial and mesodermal tissues (Fig. 3 and 4). These changes were found in the white matter of the cerebral hemispheres, the cortex and the basal nuclei being spared in the white matter of the cerebellum, including the dentate nucleus, in the midbrain, the pons, the medulla, and the cord. The lesions in the cord were severe in the cervical region but decreased in severity at lower levels. In the lumbar region there was only a slight suggestion of perivascular infiltration. The changes in the cord were most marked in the gray matter but were essentially the same as those seen elsewhere and did not primarily involve the nerve cells. In all portions of the brain and cord involved there was a perivascular infiltration with many microglia and some swelling and proliferation of the astrocytes. Although there were a few cells in Virchow-Robin's space, most of the cells were immediately outside this space in the adjacent parenchyma. The main infiltrating cell had a rather darkly staining nucleus of medium size. Many of these nuclei were irregular in shape. Rod, hooked, and boomerang forms were common. These were interpreted as the nuclei of microglia which were in an active amoeboid phase. The processes of these cells could not be stained with the silver carbonate technique. The infiltration extended out from the blood vessels into the parenchyma, decreasing in intensity and gradually merging with the surrounding normal tissue. This zone of infiltration corresponded to a zone of demyelinization which was shown in preparations stained for myelin (Fig. 5). The intensity of the demyeliniza-

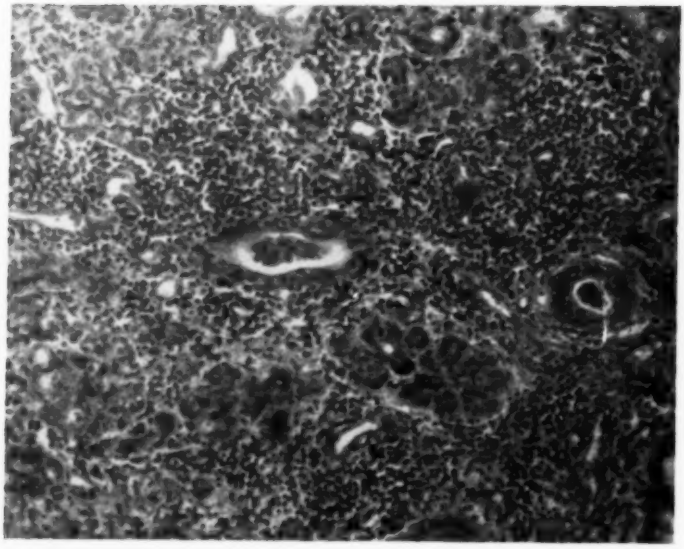

Fig. 1.—Parotid gland, Case 1. Nonsuppurative interstitial inflammation. The ducts are dilated and contain inspissated secretion. (Paraffin: hematoxylin and eosin; ×150; reduced ⅛.)

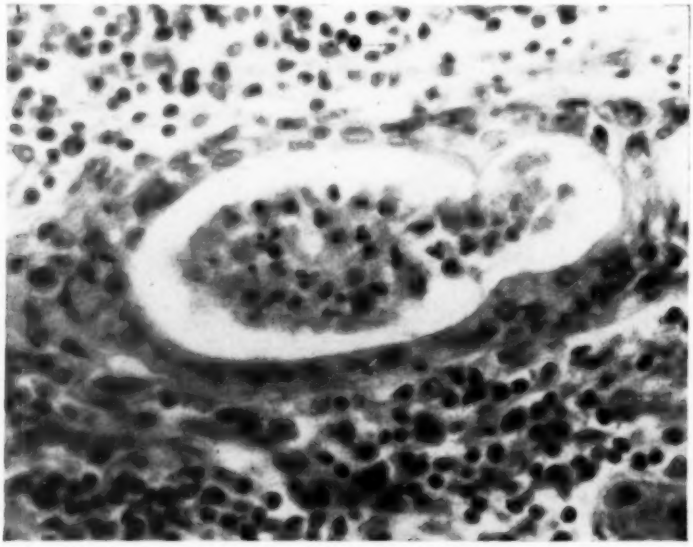

Fig. 2.—Higher magnification of Fig. 1, showing periductal infiltration with mononuclears and lymphocytes; polymorphs and debris are within the lumen of the duct. (×400; reduced ⅛.)

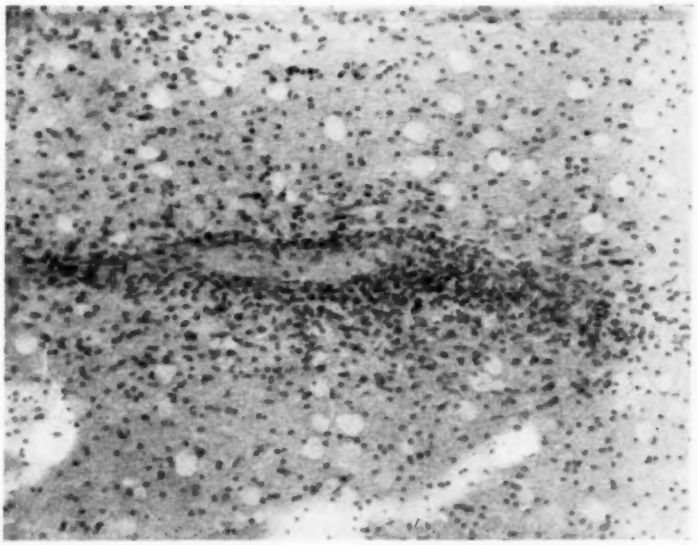

Fig. 3.—White matter of parietal lobe. Characteristic perivascular infiltration. Most of the infiltration cells are microglia and outside the perivascular space. (Pyroxylin: hematoxylin and van Gieson; ×150; reduced ⅛.)

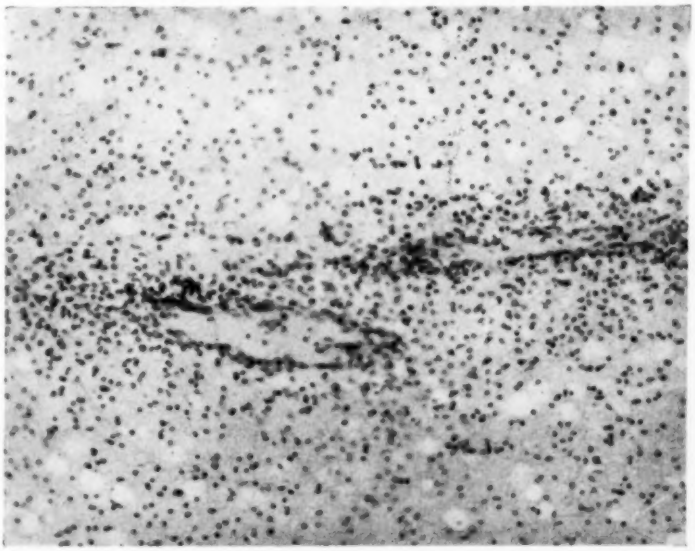

Fig. 4.—White matter of cerebellum. Characteristic perivascular infiltration. (Pyroxylin: hematoxylin and van Gieson; ×150; reduced ⅛.)

tion for the most part was in inverse relationship to its distance from the blood vessel. The myelin sheaths adjacent to the blood vessels showed all stages of degeneration, irregularity, beading, fusiform and globular swellings, and complete disappearance. The perivascular damage to the myelin in this case was not as extensive or severe as in our second case or as commonly seen in other postinfectious encephalitides. Scharlach R stain of the areas showing demyelinization revealed only an occasional cell containing neutral fat. These were present in the perivascular space and adjacent parenchyma.

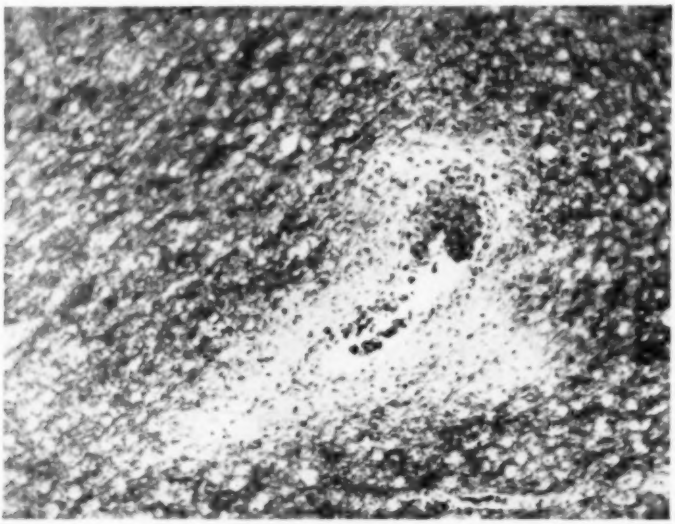

Fig. 5.—White matter of cerebellum. Perivascular areas of demyelinization. (Pyroxylin: Smith and Quigley; ×150; reduced ¼.)

There was little evidence of inflammation aside from that occasioned by the degeneration of the myelin. Polymorphonuclears were not encountered. In the gray matter of the cervical cord there were a few small perivascular hemorrhages. This was the only area in which they were found. In gray matter free or practically free of myelin, such as the cerebral cortex, basal nuclei, and cerebellar cortex, there were no demonstrable changes. However, nuclei such as the dentate and inferior olive, which contain a considerable proportion of myelinated fibers, and the gray matter of the cord showed extensive damage. In the various regions involved, the nerve cells showed some swelling and chromatolysis but were not primarily affected.

CASE 2.—The following patient was admitted to St. Catharines General Hospital, and died April 18, 1954.

G. W., a 14-year-old white boy, was admitted with a seven-day history of parotitis. For twenty-four hours prior to admission he had complained of frontal headache and pains over the eyes. On the morning of admission he could not be roused by his parents.

At the time of admission the boy was in coma and there were involuntary movements of the trunk and upper extremities. The head and eyes deviated to the right. The pupils were dilated and equal and did not react to light. The left optic disc showed early papilledema. Trismus was present. The neck was rigid. The right parotid and

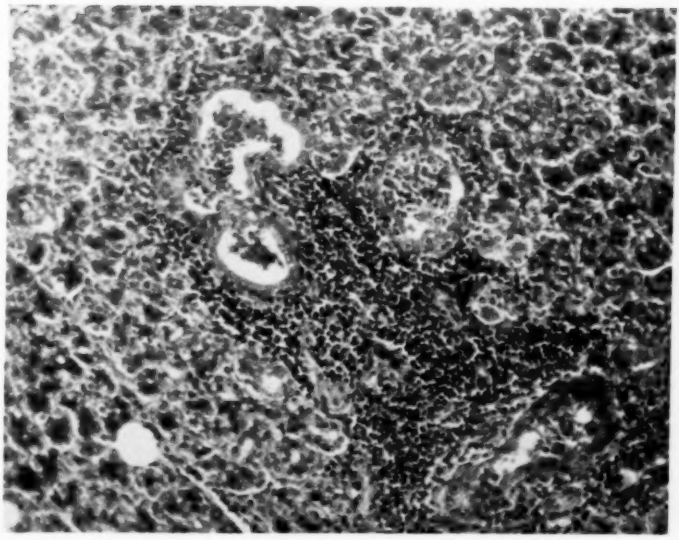

Fig. 6.—Parotid gland, Case 2. Essentially the same reaction as in Fig. 1. (Paraffin: hematoxylin and eosin; ×150; reduced ¼.)

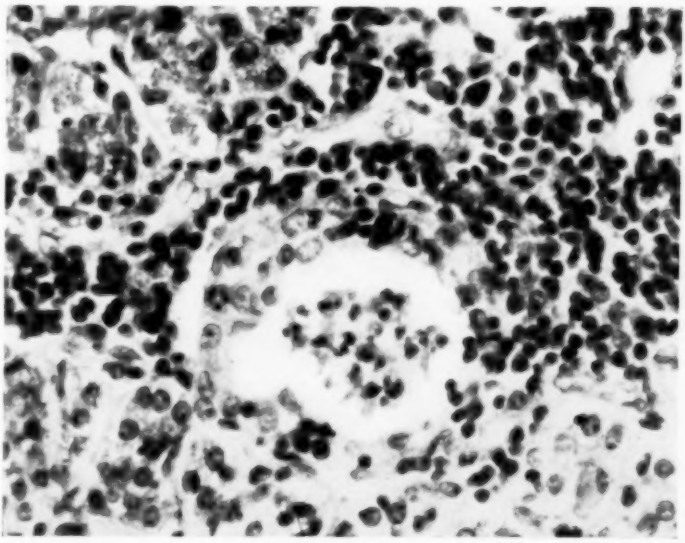

Fig. 7.—Higher power of Fig. 6. There is more necrosis of the ductal epithelium than in Case 1. (×400; reduced ¼.)

Fig. 8.—White matter of frontal lobe. Typical perivascular infiltration. (Paraffin: hematoxylin and eosin; ×150; reduced ⅛.)

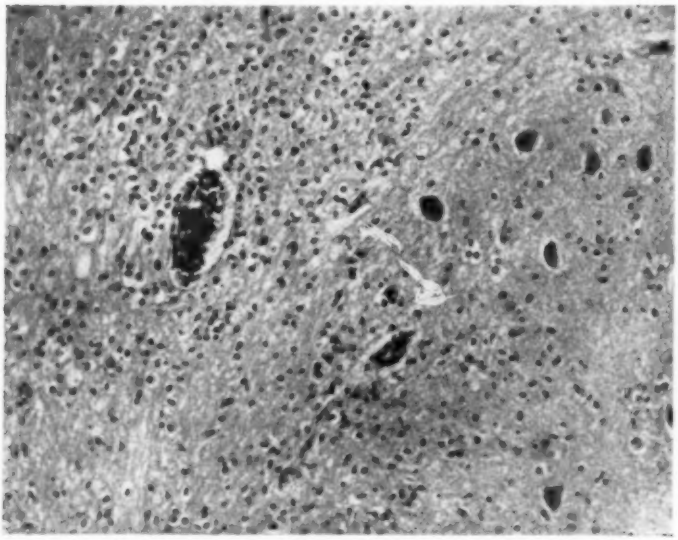

Fig. 9.—Medulla near olive. Some of the nerve cells are undergoing degeneration. (Paraffin: hematoxylin and eosin; ×150; reduced ⅛.)

left submaxillary glands were swollen. The blood pressure was 140/70. The tendon reflexes were hyperactive in the left upper extremity. The abdominal reflexes were absent in the left side. Both patellar reflexes were absent and both ankle reflexes were present and equal. Babinski and Kernig signs were not elicited.

Laboratory investigation revealed a clear cerebrospinal fluid with 180 cells per cubic millimeter. Chlorides were 815.3 mg. per cent, sugar 72 mg. per cent, and Pandy 2 plus. Culture was negative. The blood showed hemoglobin 110 per cent, red blood count 5,000,000 per cubic millimeter, and white blood count 13,500 per cubic millimeter.

The patient could not be roused. He deteriorated rapidly and died suddenly two days after admission, the ninth day after the onset of the parotitis.

Autopsy Report.—Only the positive findings will be mentioned.

Both lungs were congested and there was a patchy consolidation of the lower lobe of the right lung. The bronchi and trachea contained blood-stained froth. The right parotid gland was somewhat enlarged. The testes were not enlarged. Externally the brain appeared normal. The blood vessels were not unduly prominent, and there was no pressure coning. There was no gross evidence of exudate. The spinal cord and testicles were not removed for examination. No tissue was preserved for virus study. After fixation in formalin the cut surface of the brain at various levels showed congestion of the vessels with a suggestion of a narrow perivascular yellowish discoloration.

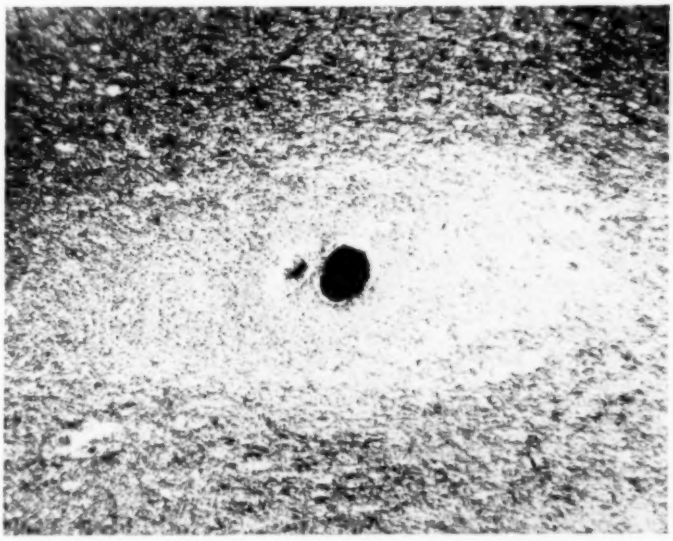

Fig. 10.—White matter of cerebellum. Perivascular areas of demyelinization. (Frozen: Smith and Quigley; ×150; reduced ⅓.)

Microscopic Examination.—Lungs: There were patchy areas of early nonspecific bronchopneumonia characterized by much edema fluid, microscopic areas of hemorrhage and scattered collections of polymorphs. *Pancreas:* Normal. *Parotid gland:* The right parotid only was available for study. This showed an interstitial infiltration with lymphocytes and mononuclears, chiefly the former (Figs. 6 and 7). This was most marked in the periduc-

tal areas. Many of the ducts were distended with inspissated secretion, desquamated epithelial cells, and numerous polymorphs. A battery of stains did not show inclusion bodies in either the epithelial or inflammatory cells. With the exception that the process appeared to be more acute, the histological features in the parotid in this boy are identical with Case 1. *Brain:* The microscopic appearances in this case were in all essential aspects similar to those present in the previous case and a description of the characteristic lesions of perivascular demyelinization need not be repeated in detail (Figs. 8 and 9). The lesions were present in the cerebral and cerebellar hemispheres, basal ganglia, midbrain, pons and medulla, and not entirely confined to the white matter. Focal areas of inflammation and acute neuronal degeneration were present in the thalamus, reticular substance of the pons, and olive. Around the degenerating nerve cells there was satellitosis with oligodendroglia and adjacent infiltration with microglia. These lesions were particularly prominent in the pons. There were a few scattered small perivascular hemorrhages and some of the smaller vessels contained hyaline platelet thrombi. In this case the perivascular demyelinization was more pronounced and the perivascular infiltration with inflammatory cells more intense and extensive than in Case 1 (Fig. 10). In spite of the extreme degree of demyelinization, fat stains revealed few macrophages containing neutral fat in or around the areas of demyelinization.

REVIEW OF OTHER REPORTS

A short review of the various reports dealing with the changes in the central nervous system will demonstrate the wide diversity of pathological lesions described and the paucity of well-documented data concerning the histological changes which occur in mumps encephalitis.

Barnes[9] described a case of a woman who developed a quadriplegia shortly after mumps. This was followed by persistent atrophy of the hands and feet. She died more than a year later of another cause. The anterior horn cells of the cervical and lumbar enlargements showed marked atrophy and degeneration. The corresponding peripheral nerves showed degeneration of their axis cylinders and disappearance of myelin. It is doubtful if the neurological changes which developed in this woman had any etiological relationship with an infection with mumps virus.

Dopter[10] describes a fatal case of mumps meningo-encephalitis and cites another by Maximowitsch.[11] In neither of these cases were histological studies done.

Bien[12] reported the case of a boy of 8 years who, eight days after an attack of parotitis, developed convulsions and died in coma twenty-four hours later. In this case there was infiltration of the perivascular spaces with compound granular corpuscles and perivascular areas of demyelinization in the white matter.

Gordon[13] published a report of four cases. There were three boys and a girl, aged 2 years, 2 years 10 months, 5 years, and 9 years, respectively. In none was mumps diagnosed clinically. In one child the parotids were found to be slightly enlarged. All the patients showed clinical signs of central nervous system involvement. In two there was an increased number of cells in the cerebrospinal fluid. At post-mortem examination all four showed an interstitial infiltration with lymphocytes in the parotid gland. Although the reproductions of the photomicrographs are not clear, the lesions appear to be similar to those seen in the cases which we encountered. The findings de-

scribed in the central nervous system were not striking nor did they have any definite characteristics. They consisted of slight and varying meningeal infiltration, congestion, and some increase in glial cells. Wasting and chromatolysis were found in a few anterior horn cells. In one case there was a perivascular infiltration with lymphocytes in one section. Unfortunately, there were no photomicrographs of the lesions in the central nervous system. As all these cases occurred during an epidemic of mumps and as the lesions in the parotid were compatible with those of mumps, it seems quite possible that these were true cases of mumps meningo-encephalitis, although they are considered doubtful by most investigators.

Acker[14] reports a 3-year-old boy who first developed swelling of the left and right side of the neck five and four days prior to onset of drowsiness. After two days of drowsiness he had a convulsion from which he did not regain consciousness. The coma persisted following admission to hospital. The cerebrospinal fluid was under increased pressure with a cell count of 90 per cubic millimeter which were mostly lymphocytes. The patient died ten days after admission, seventeen days after the onset of parotid swelling. At post mortem the brain was congested, with an increase of fluid in the ventricles. "At the base there was a meningitis with a formation of plaques of fibrin." On section (gross?) the brain substance was found to be normal. Although it was said that there was no sign of tuberculosis, it was stated that his mother died of tuberculosis nine months prior to the child's admission. Apparently microscopic studies were not done.

Larkin[15] reported the case of a male, white, aged 31 years (claimed to have had mumps three years previously) who was admitted to the hospital with clinically typical bilateral mumps. He showed evidence of cerebral involvement three days after admission. Lumbar puncture showed 300 cells per cubic millimeter; 30 per cent polymorphs, and 60 per cent lymphocytes. The patient grew worse rapidly and died seven days after admission, four days after the onset of cerebral symptoms. The brain showed an extensive accumulation of slightly turbid fluid in the cisterna magna. The pia arachnoid was congested. In many places a perivascular exudate was seen in the form of grayish-yellow lines following the course of the blood vessels. The ventricles were somewhat distended. The fluid was clear. The ependyma was slightly granular. Cultures (aerobic) from the perivascular exudate and from the spinal fluid were negative. "Microscopic sections showed the pia arachnoid to be densely infiltrated with large and small mononuclear cells. The infiltrations were definitely perivascular but also extended into the areolar tissue and the cortex. Similar cells were adherent to the arterial intima." This cannot be regarded as a typical case and the above quoted microscopic report is rather vague.

Fabian[16] reported the case of a 4-year-old child who was admitted two weeks after the onset of bilateral parotid swelling with a clinical picture suggestive of tuberculous meningitis. In the sediment of the cerebrospinal fluid there were 20 to 25 lymphocytes. No tubercle bacilli or other organism were found and the culture was negative. The patient died two days after admission. The lungs showed confluent

bronchopneumonia and caseous tuberculosis of the hilar lymph nodes. In the gross description of the brain the author described external and internal hydrocephalus. Microscopically the meninges were softened and edematous, with cellular infiltration. Focal necrosis is mentioned with perivascular infiltration of leukocytes and lymphocytes and congestion of the vessels. It was stated that there were no histological evidences of tuberculosis and the diagnosis was simple nonspecific meningitis. In view of the finding of external and internal hydrocephalus it is doubtful if this is an uncomplicated case of mumps encephalitis.

Wegelin's[17] report concerns a boy of 8 years who, eleven days after parotid and submaxillary mumps, developed signs of meningo-encephalitis. The child died in convulsions after three days. The meninges were infiltrated with lymphocytes. The blood vessels of the meninges were congested and surrounded by thick mantles of lymphocytes. The choroid plexus was congested. In the central nervous system there were numerous perivascular hemorrhages. Many of the blood vessels were surrounded by mantles of inflammatory cells, chiefly lymphocytes and swollen adventitial cells. In some places this infiltration was limited to the perivascular space. In other places it extended into the surrounding parenchyma and merged with foci of neuroglial reaction. This neuroglial reaction was, for the most part, perivascular in distribution, but sometimes it had no apparent relationship with blood vessels. These foci were associated with some demyelinization.

Cathala and associates[18] described the case of a man of 38 years who, eight days after a parotitis and five days after an orchitis, developed a diffuse and progressive quadriplegia. He died nine days later of bulbar involvement. In this case practically no changes were found in the brain and cord, and it was presumed that the lesions must have occurred in the peripheral nerves. Unfortunately, these were not examined.

Urechia[19] reported the case of a 54-year-old woman who was admitted with an acute psychosis of three days' duration. The patient became progressively worse and died six days after admission. There was no lumbar puncture. In the clinical report no mention of mumps was made until two days before death, when it was merely stated that bilateral parotitis was confirmed. The central nervous system showed irregular thickening of the meninges, congestion of the vessels and small hemorrhages both old and recent. In some places there was phagocytosis of blood pigment. The endothelium of the blood vessels was swollen. There was perivascular infiltration with lymphocytes. In the brain tissue itself there were congestion and perivascular infiltration. In the adventitia of some of the vessels there were deposits of fat. In the myelin nothing significant was found. Urechia interpreted these changes as those of a resolving meningoencephalitis from which the patient probably would have recovered if she had not died of a myocarditis. From the clinical history and the microscopic report there may be some doubt as to whether this is a true case of mumps encephalitis. The presence of a phagocyted blood pigment would indicate a lesion of some duration.

Steiner[20] records the case of a 10-year-old girl who developed meningo-encephalitic symptoms four weeks

after a bilateral parotitis. Initially, there was an irritation of the right cranial nerves. This was followed by risus sardonicus, mental changes, trismus, myotonia of the hands and the right leg, marked sweating, and salivation. Two days after admission the child died without convulsions and without disturbance of consciousness.

At autopsy, grossly the brain showed no striking abnormalities except congestion and small hemorrhages in the subcortical white matter of the parietal and occipital region bilaterally, and also in the posterior part of the right corpus striatum. These were particularly prominent in the latter region. The cord was not removed and there was no gross description of the parotid glands.

Microscopically, wide perivascular infiltration with lymphocytes and plasma cells are described in the white matter of the cerebral hemispheres. It is not stated but it is presumed that these are not limited to the perivascular spaces. Dense infiltration with neutrophils and lymphocytes was found in the basal nuclei, the pons, and medulla. This was associated with swelling of the glial cells. Occasional small hemorrhages were present. It was stated that the myelin sheaths were maintained although occasionally they showed some swelling. The pia over the midbrain was infiltrated with many lymphocytes. The parotid gland showed a moderate periductal infiltration with lymphocytes and plasma cells. A few of the ducts contained desquamated epithelium and lymphocytes. The changes in the brain were interpreted as acute poliomyelitis by the pathologist, Professor Wegelin. This is a difficult case to appraise. The lesions in the parotid seem typical of mumps virus infection. The changes in the cerebral hemispheres are unusual but not incompatible with poliomyelitis. It is presumed that Professor Wegelin saw nothing to remind him of a postinfectious type of encephalitis.

Griebel and Schnee[21] described briefly five fatal cases of so-called mumps meningitis. These were in a child 4½ years, males 28, 37, and 18 years, respectively, and a female aged 10 years. Autopsies were performed on all except the male aged 18. In all cases the bacteriology of the cerebrospinal fluid was stated to be negative. Although, in view of the rarity of the condition, this is an imposing number of cases, the value of the report is limited because of its brevity. The central nervous tissue pathology in each of the autopsied cases was merely stated to be a basal meningitis with no further elaboration.

Krauter[22] reported a fatality in a 40-year-old woman. There was an epidemic of mumps in the area where she lived, and fourteen days before the patient became ill, her three children developed mumps which in each case followed an uneventful course. Eight days prior to admission to hospital her right parotid gland became swollen and later the left. There was no apparent fever. On the day prior to her admission her husband noted a change in her behavior and that her eyes appeared to be staring. During the night previous to admission, the patient developed a high fever and became comatose. Investigation in the hospital revealed a comatose woman with slight bilateral parotid swelling. The temperature was 101.4° F., blood pressure 130/80, and pulse 100. Aside from somewhat deficient reflexes, there were no other significant physical signs.

A lumbar puncture showed 58 cells per cubic millimeter. The cells were mostly lymphocytes. Protein reaction was strongly positive. The patient was treated with penicillin with no effect. She remained comatose and febrile. Terminally, the cell count in the cerebrospinal fluid rose to 290 per cubic millimeter. She died the fifth day after admission on the thirteenth day of her illness.

The histological findings were as follow: In the parotid gland there were "signs of inflammatory infiltration." The brain showed hyperemia and edematous loosening of the tissues. The perivascular spaces were widened and contained, in addition to a fibrinous exudate, lymphocytes and a few plasma cells. In the cord there were adventitial infiltration and perivascular gliosis with destruction of myelin. The pia and arachnoid were hyperemic and there were focal lymphocytic infiltrations. In summary, there was meningo-encephalitis with perivascular infiltration of fluid and cells. There was a glial reaction and demyelinization with focal gliosis and disappearance of ganglion cells in the gray substance.

In attempting to establish a pattern for the histological changes in mumps encephalitis it seems almost incredible that there should be such a scarcity of well-documented reports. With the exception of the case previously reported by one of us (W.L.D.), in none of the papers are there photomicrographs of the lesions of the central nervous system. In many reports the description of the lesions encountered are brief, vague, and nonspecific. If all the doubtful and/or inadequately reported cases are excluded and only those considered which concerned patients who had typical mumps meningoencephalitis and who died in the acute phase of their illness, there are only three or possibly four cases aside from the two in this report on which the histopathology of mumps encephalitis can be based. These are the cases of Bien (1913), Wegelin (1935), Krauter (1953), and possibly Steiner (1942). If only these are considered, the histological picture becomes less confused and a fairly definite pattern emerges. It would seem that the preeminent microscopic findings in mumps encephalitis are in all essential features identical with that of the so-called postinfectious encephalitis with its characteristic perivascular demyelinization, and which may be associated with a variety of virus infections but is most commonly seen as a complication of measles.

COMMENT

It is considered that the pneumonic processes present in the lungs of both patients were terminal events, nonspecific, and not connected in any way with the mumps infection or the encephalitis except for contributing to the death of the patients.

The microscopic changes found in the parotid glands in both of our cases are identical and also similar to those described in the few reports concerning human material.[23] These lesions consist of periductal infiltrations with lymphocytes and mononuclear cells with degeneration and partial necrosis of the lining epithelium of the ducts and intraductal accumulations of debris and polymorphs. As our patients died eleven and nine days following the onset of clinical parotitis, the changes as seen in the parotid glands probably represent a resolving stage.

The predominent histological picture encountered in the nervous system in both of our cases, in agreement with the unquestionable cases collected from the literature, falls definitely into the well-recognized group of the so-called postinfectious encephalitides or acute perivascular myelinoclysis which may follow such diseases as measles and smallpox, and vaccination. In our second case the lesions were much more devastating and the inflammation reaction more intense than in the first. This may, in part, be explained by the fact that he died earlier in the disease process, although obviously there must be a wide variation in amount of injury to the nervous tissue in different individuals and lethal damage must be a most unusual event.

In regard to pathogenesis the problem arises as to whether the few cases of mumps encephalitis which have been fatal are extreme examples of the usually benign pathological process which is so commonly an accompaniment of mumps or is it necessary to postulate an additional or entirely different mechanism. Unless human material from nonfatal cases is available, which is very improbable, this point cannot be definitely settled. Although fatal postmumps encephalitis is much less common than lethal encephalitis following other virus infections, particularly measles, there is a similarity of time sequence, in regard to the development of neurological symptoms. The identical pathological features also suggested that their pathogenesis must have much in common.

There has been much discussion in the literature concerning the factors which may play a role in development of the postinfectious encephalitides. The various theories which have been proposed may be summarized as follows:

(a) A latent virus is stimulated or activated by the infectious disease. The chief arguments in favor of this concept is the characteristic incubation period and similar pathological findings in the encephalitis following various infections.

(b) It has also been suggested that the demyelinization is due to the activity of a hypothetic toxin liberated during the course of the disease.

(c) The changes in the central nervous system are the result of a local allergic reaction in which the virus of the associated disease in some way acts as a sensitizing agent.

(d) The etiological agent is the virus of the associated disease, probably as a result of either an augmentation or enhancement of its neurotrophic properties or a particular susceptibility of the nervous tissue in certain individuals.

In regard to (a) it would seem unnecessary to postulate a latent virus merely to explain the similarity in regard to both the clinical development and pathological lesions in these diseases. Although not associated with a demyelinating process, other encephalitides of man, such as St. Louis, and Eastern and Western equine, have like clinical and pathological patterns but are due to antigenically distinct viruses.

If the concept of a common latent virus is accepted to explain postinfectious encephalitis, it would be difficult to reconcile the variation in degree of virulence encountered, depending upon whether the latent virus was activated by vaccinia, measles, or mumps, etc. To explain the benignity of mumps en-

cephalitis in comparison with the postinfectious encephalitis associated with other virus infections, it would be necessary to postulate a characteristic or peculiar relationship or interference phenomena between the latent virus and the mumps "trigger virus."

With regard to (b), there is little to substantiate the action of a hypothetical toxin liberated by the virus infection. Superficially the perivascular distribution of the lesions in the nervous tissue might suggest the diffusion of a toxin from the blood stream.

The hypothesis (c), that the postinfectious encephalitides are due to an allergic or sensitization reaction, would seem to be attractive. Certainly the lesions produced experimentally by the injection of various components of brain tissue and suitable adjuvants are similar to those encountered in the postinfectious neurological complications. However, the experimental procedures employed to bring about these changes are highly artificial. It is likely that demyelinization can be the result of a variety of injuries and that it does not seem necessary to assume that all demyelinizing processes must have a common allergic or sensitization basis. In the experimental demyelinizing encephalomyelitis even under highly favorable conditions it commonly takes three weeks for the process to incubate, whereas in the postinfectious cases the peak incidence is around the tenth to thirteenth day after the onset of disease.[24]

Due to the great advances which have been made recently in the field of virology, circumstantial evidence is accumulating that (d) is probably the correct concept and that the postinfectious encephalites are due to, or at least occur in, intimate anatomical relationship with the virus of the associated disease.

As early as 1926 vaccinia virus was isolated from the brain of two cases of postvaccinial encephalitis,[25] and, more recently, measles virus was isolated from the brain of a boy who died of postmeasles encephalitis. Histologically, the brain showed typical lesions of perivascular demyelinization.[26] It might be argued that in these cases there was a viremia and the virus might have been present in residual blood in the brain and not necessarily be the cause of the encephalitis. The validity of this argument is lessened, however, by the finding experimentally in monkeys with mumps infection that the virus can be demonstrated by antibody labelling and by isolation from the parotids and central nervous tissue without it being present in other organs.[27] One would have expected other organs to have yielded virus if its presence in the brain could only have been explained by the presence of virus in blood. In addition, in the human being, mumps virus has been isolated at post mortem from the parotids and the pancreas or ovary but not in other organs.[23] Although no case has been reported where mumps virus has been recovered from the tissues of the central nervous system of a case of mumps encephalitis, the virus has been recovered from the cerebrospinal fluid of typical cases.[28, 29] In addition, mumps virus has been isolated from the cerebrospinal fluid of patients with aseptic meningitis diagnosed as nonparalytic poliomyelitis who had no evidence of parotitis.[30] Thus it would seem that in the case of mumps infection, if there is clinical evidence of central nervous tissue involvement, the

virus may be at least in close association with the central nervous tissue and that a contemporary viremia need not be postulated to explain its presence there. Our first case occurred prior to the development of reasonably easy methods of handling mumps virus. Unfortunately, in the second case, due to lack of local facilities, no brain tissue was preserved for virus study.

Opportunities to study fatal cases of postinfectious encephalitis are few. Unfortunately, fatal postmeasles encephalitis is not uncommon, and with the apparent development of facile tissue culture methods of isolation, handling, and identifying the virus of measles,[31] it can be anticipated that the etiological relationship of measles virus with the postinfectious encephalitis associated with that infection will soon be settled.

SUMMARY

1. The literature concerning the pathology of mumps encephalitis has been reviewed.

2. Two cases of fatal mumps meningoencephalitis with histopathological studies have been reported.

3. The fundamental lesion was a perivascular demyelinization similar to that seen in other postinfectious encephalitides.

4. It is suggested that the encephalitis may be due to the virus of the associated disease.

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ADDENDUM

Subsequent to the submission of this paper for publication, Dr. J. Godwin Greenfield of London, England, brought to the attention of one of us (W. L. D.) the report by Collins and Armour* in 1912, of an additional case of fatal post-mumps encephalitis. This concerned a boy 11 years of age who developed the first signs of encephalitis seven days after the onset of mumps. After three days of rather minor complaints of dizziness, he rapidly deteriorated and died twelve days after the onset of mumps. Accompanying the report are beautiful photomicrographs of typical perivascular lesions.

*Collins, J., and Armour, R. G.: Acute Bulbar Palsy Following in the Wake of Mumps, Rev. Neurol. & Psychiat. **10**: 361, 1912.

THE LATE EFFECTS OF LEAD POISONING

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THE late effects of lead poisoning on the physical and psychological development of children have received little attention. Though thousands of articles have appeared on lead only, Byers and Lord,[1] Elonen,[2] and Goettsch and Mason[3] have reported on the final effects of lead poisoning in patients followed for a variable period of time. The sequelae of lead intoxication in children appear to be mainly psychological. Little interference in physical development has been reported. However, two of our patients showed optic atrophy; one with permanent blindness.

During the ten-year period, 1940 through 1949, twenty-six children were treated for lead intoxication. The source of the lead was either from paint, plaster, or lead toys. Seven children (27 per cent) died, six on initial hospitalization and one two years later at another hospital with "lead encephalitis." Eleven of the remaining nineteen patients have been followed for a 5- to 10-year period during which repeated physical and psychological evaluations have been carried out, including roentgenological and chemical lead determinations. Five of the eleven patients were diagnosed and treated on an outpatient basis and the other six were hospitalized. Two of the former group were subsequently hospitalized with intercurrent infections which precipitated a return of the symptoms of lead intoxication.

To estimate the ultimate effects of lead poisoning on body and mind, an accurate evaluation of the original degree of lead encephalopathy is desirable. From the data in Table I, the hospitalized patients were empirically classified as mild, moderate, moderately severe, and severe. There is no concrete basis for such an evaluation. Blood and urine lead determinations vary with initial therapy (Cases 4 and 5). The severity of the central nervous system manifestations appears to depend on duration of lead intoxication, manner of exposure, and precipitating illness (Case 1). Details of such factors are often difficult to elicit accurately from the parents.

The symptoms in the five outpatients were vague, nonspecific, mainly gastrointestinal, and of variable duration. They are listed in order of frequency as follows: vomiting (four cases), constipation (three cases), malaise (three cases), anorexia (two cases), pallor (two cases), diarrhea (one case), irritability (one case).

The signs, symptoms, physical and laboratory findings in the six children who were hospitalized for lead encephalopathy are listed in Table I.

Except for the convulsions, all the other symptoms exhibited by the

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TABLE I

CASE	AGE (YR.) RACE SEX	CONVULSIONS	GENERAL	NEUROLOGICAL	LABORATORY	X-RAY COMPATIBLE WITH METAL POISONING	SEVERITY
1	2 ♀ W	†	Malaise Anorexia Fever Pharyngitis	Irritability	Normal blood and urine	+	Mild
2	2½ ♀ W	†	Vomiting Constipation	Hemiparesis Papilledema	Basophilic stippling. Urine lead 0.93 mg./L. CSF pressure elevated. Protein 62 mg./100 ml.	+	Moderately severe
3	2½ ♂ W	0	Vomiting	Weakness Lethargy "Meanness" Papilledema	Basophilic stippling. EEG indeterminate for age. CSF 575 mm. pressure. Protein 254 mg./100 ml.	+	Severe
Neurosurgical decompression 48 hours after admission with continuous spinal drainage for 48 to 72 hours to prevent herniation through subtemporal decompressions.							
4	2 ♀ W	0	Anorexia Pallor Constipation	Marked irritability and weakness	Basophilic stippling. EEG not disordered. Urine lead 0.227 to 4.2 mg./L. CSF 200 mm. pressure. Protein 198 mg./100 ml.	+	Moderate
5‡	3 ♂ W	†	Anorexia Vomiting	"Behavioral difficulties"	Blood lead 1.134* mg./100 ml. EEG disorganized with paroxysmal trends. CSF normal	+	Mild
6	2 3/12 ♀ W	0	Anorexia Malaise Pallor	Papilledema associated with "sprung" cranial sutures	Basophilic stippling. EEG moderately slow dysrhythmia. CSF 650 mm. pressure. Protein 72 mg./100 ml.	+	Moderate

*Normal values below 0.05 mg./100 ml.
†Normal values below 0.09 mg.
‡One of identical twins, both having lead poisoning.
Patient 5 also had hay fever, asthma, and developed a peculiar paniculitis.

TABLE II

SYMPTOMS	NUMBER OF PATIENTS	PER CENT	DURATION	AVERAGE
Irritability	8	72	2 wk.–6 mo.	1-2 mo.
Vomiting	4	36	6 wk.–6 mo.	1½ mo.
Constipation	4	36	1-2 mo.	1 mo.
Anorexia	3	27	1-2 mo.	1 mo.
Malaise	1		1-1½ yr.	
Pallor	2	18		2 wk.
Abdominal pain	2	18		2 wk.
Convulsions	3	50	Intermittent	
Papilledema	3	50	Rapid decrease 24-48 hr.	
Basophilic stippling	4	66	Disappeared 48-72 hr.	

eleven patients persisted for variable periods of time after therapy as noted in Table II.

On recent physical examination all of the children were of normal height and weight for age except one with exogenous obesity. Two of the children (18 per cent) had bilateral optic atrophy and a third had a high degree of myopia.

The x-ray findings of the long bones of the eleven patients are presented in Table III. Like the symptoms in lead poisoning, the roentgenographic changes showed a variable degree of persistence. In the entire series of twenty-six patients, complete disappearance of the "lead line" at the distal end of the shaft was eventually noted with recurrence six to seven months later in two patients. These two patients were proved to have reinstituted the paint-chewing habit. Three patients had x-ray descriptions of transverse "linear distal densities" 2 or 3 cm. from the ends of the shaft interpreted as "minimal evidence of bone growth retardation."

Urine and blood lead determinations contributed nothing to the follow-up study.

Electroencephalograms were obtained in six of the eleven patients. There was no consistency in regard to the time of the initial or follow-up electroencephalogram as related to the time of initial lead intoxication. Cases 1, 2, 9, 10, and 11 had none done. Case 3 initially was indeterminate for age, but two years later the record was consistent with organic brain disturbance. Case 4, in 1948, showed a record consistent with the age of the child. In 1954, the child had several grand mal seizures, but then became well controlled on small doses of phenobarbital. In Case 5, repeat records showed paroxysmal slow dysrhythmia for two to three years, a posterior triangle focus also being noted on the latest examination. The records of this patient have shown the greatest disorganization of the entire series and the child needs psychiatric guidance at the present time. The remaining Cases 6, 7, and 8 were almost identical in showing definite slow dysrhythmia of a variable degree.

The treatment of all patients was identical. Sodium citrate alone or with citric acid was given to maintain a slightly elevated CO_2 content (28 to 30 meq. per liter). The dosage varied from 3 to 6 Gm. daily in divided doses, for a period of from

TABLE III. RADIOGRAPHIC FINDINGS IN LONG BONES

CASE		ONSET OF ILLNESS	FOLLOW-UP 1950	FOLLOW-UP 1954
1	+	1944	0	0
2	+	1948	0	0
3	+	1948	+	0
4	+	1949	+	0
5	+	1949	0	0
6	+	1949	±	0
7	+	1949	0	0
8	+	1949	±	0
9	+	1946	+	0
10	+	1950	0	0
11	+	1949	-	0

two weeks to two and one-half years.[4, 5, 6] A summation of the follow-up is presented in Table IV.

PSYCHOLOGICAL EVALUATION

Byers and Lord note in their study of twenty children who had lead poisoning in early infancy that despite normal motor development during infancy only one child lived up to the promise of his early development. In a few children successive psychological examinations showed significant drops in intelligence quotients. These drops were thought to be the result of failure of mental development rather than actual mental deterioration. As the chronological age advanced, mental growth did not keep pace with it. In others, however, the intelligence quotient remained well within normal limits. A specific failure of development in the sensorimotor sphere was the outstanding finding. Byers and Lord felt that the lead in the circulation of an infant interferes with the changes normally occurring in the cortex and, in a high percentage of cases, prevents the normal growth and development of the cortex.

Along with the dilatory effects of mental growth, a high percentage of behavior difficulties were recorded by Byers and Lord. Such difficulties arose from an inward driveness which they classified as "forced reaction to stimuli in the environment." Strauss and Lehtinen,[7] Bender,[8] Bakwin,[9] and Stryker[10] consider this as evidence of cortical damage independent of etiology. Klebanoff and associates[11] describe the brain-injured child as hyperkinetic, overactive, restless, impulsive, and uncoordinated, but hy-

TABLE IV. SUMMATION OF FOLLOW-UP

CASE	LENGTH OF TIME SINCE EXPOSURE (YR.)	INITIAL SYMPTOMS	PHYSICAL SEQUELAE
1	10	Encephalopathy, convulsions, coma	Obesity, enuresis
2	6	Convulsions, drowsiness, encephalopathy, right hemiparesis	
3	6	Lethargy, vomiting	Bilateral optic atrophy
4	5	Irritability	Convulsions
5	5	Encephalopathy, convulsions	Abnormal EEG, behavior problem
6	5	Mild gastrointestinal symptoms. Treated as outpatient 5/49. Hospitalized 11/49 with gastrointestinal symptoms	
7	5	Encephalopathy, weakness	Bilateral optic atrophy
8	5	Gastrointestinal symptoms. Treated as outpatient	Decreased vision
9	5	Gastrointestinal symptoms. Treated as outpatient	
10	5	Gastrointestinal symptoms. Treated as outpatient. Hospitalized 6 mo. later with pneumonia 7/49	
11	5	Gastrointestinal symptoms. Treated as outpatient	High degree of myopia

pothesize that cortical maturation with compensatory development of function can occur since a less differentiated infantile cortex is involved, negating the influence of an injury which in an adult would have serious long-term sequelae.[12]

The psychological aspect of the present study was undertaken to evaluate systematically the residual psychological effects in a group of children who had had proved lead intoxication in late infancy. No records of original intellectual functioning were available prior to the poisoning. Normal mental and motor developmental progress previous to the lead intoxication was assumed in each case because of the past histories given by the parents.

Psychological testing was done in 1950 with re-evaluation in 1954. The time of the initial testing ranged from immediately after the child recovered from the lead intoxication to five years after the toxic state. Because of the immaturity of the group at the first testing it was possible only to obtain measures of intellectual and social development (Stanford-Binet intelligence scale[13] and the Vineland social maturity scale[14]).

PSYCHOLOGICAL RESULTS

Reference to Table V shows that at the time of the initial testing only two children had over-all intelligence quotients below the dull normal level, and two were in the bright average to superior categories. One of the patients below the dull normal level, Case 4, was a hyperactive, irritable child who was extremely difficult to test, and the examiner felt that the I.Q. measure of 59 was minimal. At the time of the second testing none of the children were below the dull normal level of intelligence and four were

TABLE V. COMPARISON OF RESULTS OF INTELLIGENCE TESTING IN 1950 AND 1954, OF SOCIAL MATURITY IN 1950 AND 1954, AND GOODENOUGH I.Q. IN 1954 FOR ELEVEN CHILDREN WHO HAD LEAD POISONING

CASE	AGE AT ONSET (YR.)	1950 CHRONOLOGICAL AGE (YR.)	BINET I.Q.	INTERMEDIATE TESTING	1954 CHRONOLOGICAL AGE (YR.)	BINET I.Q.	GOODENOUGH I.Q	1950 VINELAND I.Q.	1954 VINELAND I.Q.
1	2	7.4	106		11.5	109	65	115	114
2	2½	4.1	86		8.1	88	86	116	102
3	2½	4.3	Appeared normal		8.3	99	Blind	87	83
4	2	3.1	59	74	7.1	88	74	76	100
5	3	3.3	127	137	7.6	110	73	73	105
6	2½	2.1	100		6.6	122	112		127
7	2 3/12	3.1	82		7.3	87	83	95	105
8	2 1/12	3.1	78		7.1	84	98	89	98
9	2	3.1	97		7.3	99	99	105	105
10	2				6.3	111	91		111
11	1 1/12	2.6	116		6.7	125	90	116	105
Mean	2.03	3.1	93.77		7.6	102.00	85.1	99.11	105.00
Standard Deviation			18.37			13.76	4.08	13.71	10.31

Rank order correlation between 1950 and 1954 I.Q.'s .08

T-Test between 1950 and 1954 I.Q.'s (corrected for correlations) 2.12*

Rank order correlation for Binet and Goodenough I.Q.'s 1954 .05

T-Test for Binet and Goodenough I.Q.'s 1954 (corrected for correlations) 3.28†

*Significant at .05 level of confidence.
†Significant at .01 level of confidence.

in the bright average to superior categories. The bright average to superior children showed little unevenness in their functioning. The type of items most frequently failed by the children in the dull normal category were items involving abstract thinking. Although this is a characteristic failing of children with brain damage, it is also the type of thinking which would be expected of children with dull normal intelligence natively. Three of the eleven children showed some difficulty copying a diamond at the seven-year level, but there was no conclusive evidence in the over-all intellectual functioning characteristic of children with brain damage.

It is recognized that intelligence tests, made at different times on the same individual, may vary as much as ten points on the basis of chance factors alone. Reference to Table V shows that I.Q. changes in three of the eleven children (Cases 4, 5, 6) were significantly greater than would be expected by chance. Two of these showed improvement, while one went down. However, with the exception of Case 5 who decreased, all of the other children showed an increase of from 2 to 9 I.Q. points. The difference between the average I.Q. of 94 at the time of initial testing and 102 at the time of the last testing shows an improvement in intellectual level which is significant at the .05 level of confidence (would be expected to occur on the basis of chance only five times out of 100). A continuing intellectual decline after the initial testing, as expected from the results of Byers and Lord, was not found in our series. Instead, there was some evidence of an actual increment in intellectual functioning.

Even greater significance is added to this finding when it was realized that the one child who showed a decrease in intellectual functioning was under psychiatric care. A complete psychological study on this boy three months previously was summarized as showing: "Severely neurotic personality structure characterized by marked anxiety, regressive and repressive trends in a child of superior intelligence (I.Q. 126). Emotional problems are affecting functioning and relationships. There are also some organic indications which need further evaluation. Treatment assets are: superior intelligence, ability of ego to maintain itself despite stress, conformity and the anxiety itself."

It seems possible that the decline in functioning ability in this one case was due, at least in part, to a functional psychological disturbance.

On both testings, social development, as measured by the Vineland Social Maturity, was somewhat above intellectual development. Although these differences were not significant, the suggestion is present that these children are somewhat better able to perform in practical everyday situations.

On the second testing, however, the intellectual measure obtained from the Goodenough draw-a-man test[15] was significantly lower than that obtained from the Stanford-Binet intelligence scale at the same time. The difference between the average Goodenough I.Q. of 85 and the Binet I.Q. of 102 was significant at the .01 level of confidence. Though the drawing test primarily measures visual-motor functioning, while the intelligence scale is primarily a verbal test,

the significant positive correlation which has been demonstrated between these two tests indicates that they measure two types of behavior which tend to develop at similar rates. The correlation of .05 between these two measures for this group would indicate that there is no relationship other than chance between the developmental rates of these two types of behavior for these children. In other words, it would seem that while the over-all intelligence of these children remains intact and is developing normally, a definite deficit is seen in their visual-motor functioning. Furthermore, qualitative analysis of the drawings revealed the disorganization in body image and immature drawings which Silver[16] describes as characteristic of children with brain damage.

TABLE VI. 1954 GRADE PLACEMENT, SCHOLASTIC ACHIEVEMENT, AND RESULTS OF VISUAL-MOTOR TESTS OF BRAIN DAMAGE OF ELEVEN CHILDREN WHO HAD LEAD INTOXICATION IN INFANCY

CASE	GRADE	1954 EDUCATIONAL LEVEL	1954[20] WIDE RANGE ACHIEVEMENT		GRAHAM-KENDALL CATEGORY	BENDER-GESTALT
			READING	ARITHMETIC		
1	5	Failed second grade. Doing well now except arithmetic	6.0 grade	3.6 grade	Borderline	Rotated designs, A and 3; difficulty with spatial relations
2	2	Held back ½ grade	2.5	2.3	Normal	Normal
3		Blind, in school for blind	Blind	Blind	Blind	Blind
4	2	School problem	1.1	1.1	Brain damaged	Reversed A; rotated 8; primitive loop and lines; difficulty with angulation
5	3	School problem	2.1	2.3	Brain damaged	Rotated designs A, 3, 4, 5, 8; primitive loops, difficulty with angulation
6	2*	Does well	1.2	1.4	Borderline	Rotated designs A, 3; perseverated on 1 and 2; primitive loops, difficulty with angulation
7	1	Held back 1 grade	1.0	1.4	Brain damaged	Perseveration; poor spatial relations, difficulty with angulation on 7 and 8
8	1	Held back ½ grade	1.3	1.3	Brain damaged	Primitive loops and lines; poor spatial relations; difficulty with angulation on 7 and 8
9	2	Held back ½ grade	1.6	1.5	Brain damaged	Rotated designs 3, 4, 5, 7; difficulty with angulation on 7 and 8
10	1*	Does well	0.9	1.4	Normal	Perseveration in design 2, primitive loops and difficulty with angulation
11	2*	Does well Poor in drawing	2.5	2.7	Brain damaged	Spatial relations poor on a 2, 4; difficulty with angulation on 7 and 8

*Reported to be doing well in school.

It is of interest, then, to note, that despite intellectual functioning within the normal range, only three of the eleven children are reported by their mothers to be doing well in school. (See Table VI, Cases 6, 10, and 11.) Two of these patients (Cases 6 and 10) show academic achievement below their grade placement, which suggests that they are actually having more difficulty in school than has been reported by their parents.

Tests of visual-motor functioning which are specifically designed to measure behavior characteristic in the individuals with cortical damage reflected considerable deficit in this area. On the Graham and Kendall[17] visual motor test with correction for chronological age, Cases 2 and 10 were within normal category: Cases 1 and 6 were in the borderline brain-damaged category; and Cases 4, 5, 7, 8, 10, and 11 showed visual-motor deficit within the brain-damaged category. At the extreme end of the continuum of visual-motor deficit was Case 3 who is totally blind as a result of the lead poisoning.

An even more-pronounced deficit was noted in the group's performance on the Bender-Gestalt visual-motor test.[18] Case 2 was the only child who was able to copy the designs of this test in a fashion which was normal for her age level. All of the other children showed the rotation of designs, perseverations, difficulty with angulation, and substitution of primitive loops and lines for dots which Silver[16] describes as characteristic of children with brain damage.

Case 2 is the one child in this group of eleven, then, who does not show a visual-motor deficit. This is of particular interest when it is remembered that her toxic reaction was one of the most severe, and at the time of her hospital admission she suffered a left hemiplegia. This suggests that there is no direct correlation between the severity of the toxic reaction and the severity of the residual effects reflected in the psychological functioning.

A closer consideration of the type of errors made by these children in their visual-motor functioning shows behavior which is paralleled in their academic achievements. The rotations of their drawings of designs placed directly in front of them suggest that these children would find it difficult to learn to read in a teaching situation which requires them to recognize the visual picture rather than paying attention to the phonetic elements of the word. This was borne out in their reading tests by a considerable number of reversed letters, reversal of whole words, and of misrecognition of words due to attention to the first letters.

DISCUSSION

Thorough physical and laboratory examination revealed little that could be attributed to the late effect of lead intoxication in a group of children followed for a five- to ten-year period of time. The effect of increased intracranial pressure in Case 3 resulted in blindness as the only physical residuum in the whole group.

However, the organic brain damage that resulted is only apparent in the specialized psychological tests done repeatedly, and the results are quite similar to those seen in children with brain damage due to birth injuries or, more specifically, cerebral anoxia.

From previous pathological studies of our own and others, serious vascular damage, cerebral edema, with resulting cortical injury, is the underlying basis for the picture of lead encephalopathy.[19] The intellectual degradation as reported by Byers and Lord is not confirmed and the outlook should be definitely more hopeful.

It would seem that these children with visual-motor deficit are placed in an extremely frustrating position during their primary grades. Though their learning capacities are within normal range, the visual-motor deficit presents a serious handicap to the child in the present school system. The presentation by visual stimuli for learning is frustrating. Special tutoring in this one area or placement in a school situation which would allow the use of other sense modalities in learning, such as phonetic or kinesthetic approaches, might minimize this frustration.

Case 5 is presented in support of this hypothesis. Though the pathology in his home situation cannot be denied, the intermediate testing prior to entrance to school yielded an I.Q. of 137. During three school years, his teachers complained that he was "a negativistic, restless, poorly attentive child, who refused to learn." Because of such behavior and because of the general family situation, psychiatric help was advocated. The extremely frustrating situation presented to a boy of superior intelligence who is handicapped in learning by poor visual-motor coordination cannot be overlooked. This handicap might be a contributory factor in his need for psychiatric help.

The pictures presented by Cases 1 and 3 are more hopeful and suggest that, with understanding help, the children may learn to adapt to the deficit. Case 1 is the oldest child in the series and her lead intoxication occurred ten years prior to the last evaluation. She has attended parochial school and has received a good deal of individual attention. The primary grades presented difficulties characteristic of any brain-damaged child and there was failure to pass the second grade. Her mother reports that she is doing well in school now, but is slow in arithmetic. Her achievement test scores corroborate this, as she is at her grade level in reading but is retarded in arithmetic. The visual-motor deficit is not as pronounced as in many of the other cases. This suggests that the effects of cortical injury may be negated as the central nervous system matures. Patient 3 is totally blind and has been receiving training at the Missouri State School of the Blind. Neither difficulties in the primary grades nor the behavioral troubles are as marked as in the other children.

At the time of the initial testing five of the children presented the driven, negativistic, hyperactive behavior which is characteristic of children with brain damage. None of the children displayed this type of behavior at the time of the final examination. Cooperation was excellent, even with the boy who is under psychiatric care. It was only when his mother entered the room that his negativism was evidenced. The one common personality trait exhibited by the group was that of strong motivation to achieve in all tasks, with repeated voicing of fears that they were

not doing well or might fail. Such dissipation of hyperactivity or inward driveness with cortical maturation associated with some types of brain damage concurs with previous reports by other authors.

The attitudes of the mothers toward these children were of interest. The fact that eleven mothers out of a possible nineteen brought their children in for re-evaluation is an evidence of their conscientiousness. In most of the cases there appeared to be an overprotective attitude. The mother of Case 1 wondered if she "babied her daughter too much" and feared the family was overprotective. The child is obese and enuretic. Case 2's mother has showered an unusual amount of attention on her child "because she has been so sick." The child's teachers complain that "she acts up in school and refuses to obey," although the mother denies this problem at home. The mother of Case 5 wondered if her son's fearfulness, excessive sense of guilt, and "sissy behavior" were the result of lead intoxication and admitted the need of protecting him because of his lack of assertiveness.

The parents naturally assume a certain amount of responsibility for the lead intake and resulting lead intoxication. Such responsibility is associated with consequent guilt feelings and is reflected in the overprotectiveness of many of the parents in this series. Pediatric counseling of the parents of children with lead intoxication should help them with their subsequent attitudes and do much to prevent the development of additional personality problems. Realization of the visual-motor deficits in these children should be of aid to their teachers and prevent to a certain extent the development of problems as just described.

SUMMARY

Eleven cases of lead intoxication have been followed for a period of from five to ten years with repeat physical, psychological, and laboratory examinations.

The physical sequelae consisted of blindness and cerebral dysrhythmia.

Sodium citrate was the specific therapy in all cases and was given over a variable period of time or until there was no laboratory evidence of lead intoxication.

There is no evidence in this series of continuing mental deterioration. Considering the major mode of instruction in the primary grades, it is felt that these children are at a serious disadvantage and should receive special attention to offset their visual-motor deficit. As the child matures there is a gradual loss of the inward driven hyperactive behavior frequently seen in brain-damaged children. There is no direct correlation between the severity of the illness and the amount of residual effect.

Pediatric counseling might be influential in reducing a parenteral overprotective attitude which adds to the child's problems.

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A Problem in Neurosurgery

September 1644. One of the deacons of Boston church, Jacob Eliot had a daughter of eight years of age, who being playing with other children about a cart, the hinder end thereof fell upon the child's head, and an iron sticking out of it struck into the child's head, and drove a piece of the skull before it into the brain, so as the brains came out, and seven surgeons (some of the country, very experienced men, and others of the ships, which rode in the harbor) being called together for advice, etc, did all conclude, that it was the brains, (being about half a spoonful at one time, and more at other times,) and that there was no hope of the child's life, except the piece of skull could be drawn out. But one of the ruling elders of the church, an experienced and very skilful surgeon, liked not to take that course, but applied only plasters to it, an withal earnest prayers were made by the Church to the Lord for it, and in six weeks it pleased God that the piece of skull consumed, and so came forth, and the child recovered perfectly; nor did it lose the senses at any time.

WINTHROP'S JOURNAL 1630-1649. J. K. HOSMER, EDITOR. New York, 1908.

RADIATION NEPHRITIS

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RADIATION nephritis as a clinical entity has, until recently, been discussed principally in the experimental literature. A survey of the major pediatric textbooks in this country[1-4] has failed to reveal any recognition of this disease as a specific entity. Campbell,[5] in his textbook, mentions the condition "radiation nephritis" but gives no particulars concerning its manifestation. Because of the lack of attention to this condition it was thought that a review of the literature of radiation effects on the kidney and a case report of this disease would be of some value.

REVIEW OF THE LITERATURE

In less than a year following the first description of the x-ray by Wilhelm Konrad von Röntgen in 1895,[6] there were several reports of deep tissue effects of these rays.[7-9] Walsh[10] reported several cases in which symptoms arose from abdominal organs in persons exposed to roentgen rays. Linser and Baerman,[11] working with rabbits, found that exposure of the kidneys to roentgen rays produced a transitory albuminuria but found no apparent changes in the renal epithelium on microscopic examination.

Schleif and Hildebrand[12] and Linser and Helber[13] noted evidence of effects of roentgen rays on the kidneys manifested by increased urinary excretion of uric acid. Both of these investigators felt that the increased excretion of uric acid was not due to the effects of the rays on the kidneys themselves but was due to toxins produced by the destruction of other body tissues.

Buschke and Schmidt[14] and Schulz and Hoffman,[15] working with rabbits, brought the kidneys to the body surface and irradiated them for varying periods of time. Both investigators found gross changes in the kidneys seven to eight weeks following the exposure. In Bushke and Schmidt's[14] material several of the animals showed albuminuria but no pathologic changes, while in a few animals dying seven to eight weeks following the irradiation, they were able to show necrosis of both the cortex and medulla of the kidney. In Schulz and Hoffman's[15] material the kidneys were examined microscopically at intervals of one hour to forty-eight days following the roentgen-ray exposure. They found early changes of hemorrhage and transudation but later changes of tubular destruction and increased interstitial tissue. They stated that the findings at the end of forty-eight days resembled the picture of an early "chronic interstitial nephritis."

Krause[16] and Krause and Ziegler[17] denied any effects on the kidney from roentgen-ray exposure; however, Rosenstern[18] and later von Jaksch[19]

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reported albumin in the urine of patients following their exposure to roentgen rays. Edsall[20] as early as 1906 stated that, "In those patients who already have nephritis or those whose kidneys are under especial strain, x-ray exposure should be guardedly used or e x c l u d e d." Warthin[21] cited several cases where extensive x-ray therapy was given for leukemia, following which some degree of renal injury was noted, manifested by deposits of lime salts, atrophic changes, and fatty degeneration of the kidney. It was also noted that the kidney showed an increase in intertubular connective tissue. Edsall and Pemberton[22, 23] and Heymann[24] found marked nitrogen retention in patients and in experimental animals following exposure of the kidneys to x-rays.

There were no further reports on the effects of roentgen rays on the kidneys until there appeared a group of papers by Hall and Whipple,[25] Stephan,[26] and McQuarrie and Whipple,[27] all of whom noted transitory decrease in excretory function of the kidney immediately following irradiation but found no microscopic evidence of damage to the kidney, and concluded that the x-ray did not produce nephritis.

However, Martin and Fisher[28] and Kalodny[29] irradiated the kidneys of dogs and rabbits, respectively, and found slight but definite microscopic changes in the kidney, suggesting a definite effect of the x-rays. Martin and Fisher[28] thought the changes they observed in dogs were suggestive of "interstitial nephritis."

In 1926 and 1927 a series of articles were published by Hartman[30] and Hartman, Bolliger, and Daub[31, 32] dealing with the effects of radiation on the renal tissue of dogs. They showed that renal tissue was quite sensitive to radiation and that experimental nephritis could be produced with varying doses of radiation. In some of their experiments they were able to produce nephritis with doses so low that epilation did not follow the exposure. They described the clinical picture and pathologic changes in the kidneys of their animals which closely anticipated the findings later described in man. In 1927 Daub and associates[33] reported two clinical cases of their own and reviewed sixteen cases collected from several sources in whom nephritis developed during or after a course of deep x-ray therapy over the kidney area.

O'Hare and co-workers,[34] Tsuzuki,[35] Gabriel,[36] Domayk,[37] and Willis and Bachem[38] all reported pathologic changes noted in the kidneys following x-ray irradiation. All of these authors commented on the fact that the changes were of a progressive nature and noted that the tubular structures were much more seriously involved than were the glomeruli.

Domayk[39] was probably the first person to describe the lesions of radiation nephritis in a child. The child, a girl aged 9 years, erroneously received a large dose of unfiltered radiation over the kidney area. There were erythema and vesication of the skin and an almost immediate reaction characterized by albuminuria and casts in the urine. The patient died six months later with symptoms of renal failure.

Warren[40] reviewed the then current literature on x-ray radiation effects on the kidney.

In 1930 another series of articles appeared dealing with the experimental production of renal disease by the use of the x-ray. Bolliger and co-workers[41-44] described the clinical and pathologic findings of lesions of the kidney produced by x-rays. In these articles the progressive nature of the renal lesion is stressed. It was the opinion of the authors Bolliger and Laidley[41] that in the work of Krause,[16] McQuarrie and Whipple,[27] Linser and Baermann,[11] Buschke and Schmidt,[14] and Hall and Whipple[25] no pathologic lesions were demonstrated because they examined the kidneys during a latent period in the development of the condition.

Baumann[45] and Enger and Preuschoff[46] continued the reporting of definite pathologic lesions produced by exposing the kidneys to x-rays. Adams and associates[47] reported on "Experimental Chronic Nephritis Produced by Radium." They reported that the changes observed in the kidneys were comparable, in many respects, to what was seen in the kidneys of human beings with chronic hypertensive nephritis.

Hagner and Coleman[48, 49] reported a case of suppression of urine following massive doses of x-ray. Desjardins,[50] Impiombato,[51] and Elwood and Belair[52] reported on the relative insensitivity of the kidney to x-rays, recognizing, however, that the kidney could be damaged by irradiation. Page[53] produced nephritis in dogs by the use of roentgen rays and called the disease "roentgen-ray nephritis." Wharton[54] and Waters[55] stated the case for the preoperative irradiation of tumors of the kidney. Munger,[56] employing irradiation as an adjunct in the treatment of malignant renal neoplasms, found that the therapeutic dosage he used had an irritating effect on the remaining single kidney but he considered this only transitory. However, he warned, "Irradiation in the dosage used has a very marked latent depressant effect in the acquired single kidney already damaged by nephritis. Unanticipated, this may cause death."

Mertz and collaborators[57] found definite changes which they attributed to irradiation in the unaffected parts of the kidneys irradiated for malignant tumors. Again in 1942 Warren[58] reviewed the then current literature on the effects of radiation on the urinary system and summarized the renal changes due to radiation as reported up to that time. Zollinger[59, 60] reported the findings in mice of hypertension following the irradiation of the kidneys and tried to correlate the peaks of the hypertension with the microscopic picture he observed at the time the peaks occurred. Mendelsohn and Caceres[61] studied in detail the effects of x-rays on the renal function in dogs and found that the tests for tubular function, using the maximal tubular excretion of para-aminohippurate, showed a prompt depression following exposure of the kidneys to varying doses of x-rays and that the depression was proportional to the dosage used.

In 1944 Dean and Abels[62] reported a case in which they noted hypertension in a 20-year-old woman which they felt was brought about by the

effects of irradiation of a single kidney. Beginning in 1950, with a paper by Zuelzer and associates,[63] the clinical picture of radiation nephritis began to assume the aspect of a definite clinical entity. Zuelzer's report dealt with three children in whom he noted a similarity of clinical course following exposure to x-rays, which he called probable radiation nephritis.

Paterson[64] and his colleagues Kunkler, Farr, and Luxton[65] emphasized the great danger of damage to the kidney when both kidneys receive a dose exceeding 2,300 r in five weeks or less. These authors observed patients who had been treated by x-ray bath for seminoma testis. Luxton[66] carefully described the clinical and clinicopathologic features of radiation nephritis, utilizing the cases reported earlier by his group.[64, 65] Later Carpender[67] reviewed the work of the Manchester group and sounded a note of warning concerning the dangers of overradiation of the kidneys.

In the following case, radiation nephritis developed in a 9-month-old boy as a result of postoperative irradiation, following a nephrectomy for Wilms's tumor.

CASE REPORT

The patient was born at the Chicago Lying-in Hospital following a normal pregnancy and an uneventful labor and delivery. His postnatal course was without incident and no abnormality was noted during the neonatal period. He was next seen in the clinic at 9 months of age with a twenty-four-hour history of temperature elevation to 103° F. rectally. He had been seen by his family physician who had diagnosed bronchitis, but in the course of the physical examination found a large mass in the left side of the abdomen, and referred the patient to the Bobs Roberts Hospital. The patient had seemed otherwise well.

Physical examination at the time of admission, April 24, 1954, revealed an active 9-month-old boy who did not appear ill. His pulse rate was 100 per minute and his rectal temperature was 37.2° C. The only positive physical findings were a protuberant abdomen and a large, firm, nontender mass occupying the left upper quadrant and extending posteriorly with its upper border easily palpable. The liver was palpable 2 cm. below the right costal margin. Laboratory data revealed white blood cell count of 12,950, 39 per cent polymorphonuclear leukocytes, 57 per cent lymphocytes, 3 per cent monocytes, 1 per cent eosinophils hemoglobin 11.7 grams per 100 c.c., red blood cell count 4.56 million.

Urinalysis was within normal limits, no albumin, no abnormal microscopic findings. On April 26 the blood urea nitrogen was 24.7 mg. per cent and the nonprotein nitrogen was 40.5 mg. per cent. An intravenous pyelogram was done on April 24, which revealed a mass in the left perirenal area displacing the left kidney anteriorly and the left ureter medially. The calyceal system was not well visualized on the left. The right calyceal system and ureter appeared normal and excreted the dye (Urokon) well.

A left nephrectomy was performed on April 26. The specimen was examined by the pathologist and the final diagnosis was that of Wilms's tumor of the left kidney, of the tubular cystic and papillary cystic adenocarcinomatous type. There was no demonstrable invasion of the veins at the hilus or of the pelvis. Preoperatively the patient was given irradiation over the upper abdomen in the region of the left kidney consisting of 1,000 r depth dose, through 10 by 10 cm. portals anteriorly and posteriorly. Postoperatively irradiation

was given by a lower thoracic and upper abdominal bridge (15 by 20 cm.). The x-ray therapy was begun on the third postoperative day, April 29, and the patient received a treatment each day until May 3, at which time the course was interrupted because of melena. The bleeding stopped spontaneously in about six days, and on May 10 the x-ray treatments were resumed. The last treatment was given on May 19 at which time the patient had received 2,000 r over the bridge area. The white blood cell count was followed carefully during the period of x-ray therapy and the lowest count observed was 5,750 on May 16, at which time he had 80 per cent polymorphonuclear cells, 11 per cent lymphocytes, 4 per cent monocytes, 2 per cent basophils, and 3 per cent eosinophils. Repeated x-rays of the chest were taken which showed no definite lesion. Postoperatively on April 30, a small area of pneumonitis or atelectasis appeared in the right lower lobe. However, all subsequent x-rays of the chest were normal.

The patient never did well following nephrectomy and irradiation. He failed to gain weight, his appetite was consistently poor and he tired easily. Although he was playful, he appeared frail and wan. He was sent home on May 28, 1954, and remained there three months during which time he became progressively more anemic, his hemoglobin falling from 12 to 6.9 grams.

The boy was readmitted to the hospital on Aug. 31, 1954, four months after his nephrectomy and irradiation. The complaints at that time were swelling of his face and swelling of his feet. Physical examination revealed a thin, pale, weak child with edema of the dorsum of both feet and a puffy appearance to his face. His blood pressure was 128/90, pulse rate 108 per minute, respirations 50 per minute. Laboratory data showed 6,700 white blood cells with 48 per cent polymorphonuclear leukocytes, 49 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils, hemoglobin 6.9 grams per 100 c.c., red blood cell count 2.34 million. Urinalysis revealed albuminuria, occasional hyaline and granular casts, 25 red blood cells per high-power field, and 0 to 2 white blood cells per high-power field. These urinary findings persisted. On September 2 the nonprotein nitrogen was 78 mg. per cent, and on September 7 twelve-hour urea clearance was 11.5 per cent of mean normal by the square root formula.

On September 7 the patient's blood pressure rose to 176/144 and for the rest of his hospital course continued to range from 170 to 180 systolic and 120 to 140 diastolic. On September 13 the nonprotein nitrogen was 92 mg. per cent. The following day the patient was transfused with 100 c.c. of packed red cells over a five-hour period. However, five hours following the transfusion the boy developed all the signs of acute heart failure. He was digitalized and a course of 50 per cent magnesium sulfate was given to reduce the blood pressure but was not effective. The patient had a steady downhill course, with progressive signs of renal failure. On September 16 the patient seemed very confused and was thought to have hypertensive encephalopathy. On Sept. 17, 1954, he had a generalized major convulsion and died.

Pathologic Findings.—At post-mortem examination the gross findings revealed the spleen to be adherent to the abdominal wall with dense fibrous adhesions. The left kidney was surgically absent, the left adrenal was hemorrhagic and fibrosed to the scar tissue, involving the spleen. There was about 50 c.c. of clear yellow fluid in the abdomen. The small bowel contained a number of small telangiectatic vessels more numerous in the proximal jejunum near the ligament of Treitz.

The pericardial cavity contained 20 c.c. of straw-colored fluid and the heart weighed 95 grams (normal for

the age is 45 grams). The left ventricle was hypertrophied; the right atrium was moderately distended. There were many small pericardial hemorrhages.

The lungs showed moderate edema throughout. The pleural surfaces were smooth but contained multiple recent scattered focal hemorrhages. There were many small focal hemorrhages scattered throughout the parenchyma of both lungs.

The pancreas was hemorrhagic throughout with increase in the connective tissue and small focal areas of softening. The left lobe of the liver was atrophic. There were small scattered focal hemorrhagic areas and two large areas of hemorrhage in the gastric mucosa. The proximal jejunum near the ligament of Treitz was diffusely edematous and contained focal areas of mucosal hemorrhage and dilated serosal vessels. There were a number of small hemorrhagic areas in the mucosa of the cecum.

The left adrenal appeared black. The cut surfaces showed both the medulla and cortex to be hemorrhagic. The right adrenal appeared normal although there seemed to be some thinning of the cortex.

The right kidney weighed 41 grams (normal for age is 36 grams). The capsule was stripped with ease. The capsular surface was granular and reddish brown in color, with approximately a dozen small scattered petechiae over the surface. The cut surface did not bulge. The cortex appeared normal and the division between the cortex and the medulla was sharp. The medulla appeared moderately hypertrophied. The pelvis and calyces appeared normal except for mucosal hemorrhages. The brain grossly was not remarkable.

On histologic examination there were widespread recent hemorrhages, most extensive in the atrophic left lobe of the liver, in the pancreas, stomach, jejunum, left adrenal, and lung. The liver cords were swollen and there was scattered infiltration of the sinusoids with polymorphonuclear cells. The left lobe contained large areas of lobular atrophy with hemorrhages into these areas. The left adrenal showed areas of atrophy with destruction of the cortical pattern and hemorrhages into these areas. There were extensive extracapsular hemorrhage and occlusion of capillaries by fibrinoid material. The pancreas had areas of severe necrosis in many focal areas with intra-alveolar hemorrhage as well as hemorrhage into the peripancreatic fat. There was also marked arteriosclerosis.

Bone marrow taken from the lower lumbar region was very cellular; however, the lower thoracic vertebral marrow showed large fatty areas with areas of regenerating hematopoietic tissue.

The histologic findings in the right kidney were quite striking. The glomeruli were enlarged, bloodless, and the loops were fused and occluded by fibrinoid and amorphous material. Many of the glomeruli were partially hyalinized and there was much nuclear variation with some giant nuclei. Most of the glomeruli were involved. Fat stains demonstrated small droplets of fat in the occluded loops. There were atrophy, dilatation, hydropic change, colloid droplet change, and necrosis of the tubules. There were hyaline, granular, and calcium casts seen. Both tubule cells and casts contained lipid material. The arterioles and small arteries were sclerotic with hyaline obstruction of many of the lumina.

The final pathologic diagnosis was that of radiation nephritis; postirradiation changes of the left adrenal, stomach, proximal jejunum, lungs, left lobe of the liver, and pancreas; uremia with widespread recent hemorrhages most extensive in the atrophic left lobe of the liver, pancreas, stomach, jejunum, and left adrenal; surgical absence of the left kidney with removal of a Wilms's tumor with no evidence of recurrence.

DISCUSSION

The general acceptance of x-ray therapy following the surgical removal of a renal neoplasm has led to a gradual increase in dosage over a wider area in an attempt to increase the survival rate. With the increased dosage over a large area has come the realization that important abdominal organs, especially the kidneys, can be seriously and permanently damaged by the irradiation and that this damage can cause the patient's death.

Zuelzer and associates[63] set the stage for the recognition of radiation nephritis as a clinical entity. They believed that the changes found in the kidney on microscopic examinations, which were similar to the changes previously detailed, constituted a distinctive picture. It was further pointed out that the survival periods, reckoned either from the onset or from the time of completion of radiation therapy, were remarkably similar in their three cases. (See Table I.) Zuelzer[63] made note of the size of the portals and the possibility that, even though the principal area of irradiation was that of the extirpated kidney, the remaining kidney must have received a substantial amount of radiation. The fact that in Cases 2 and 3 in Table I hypoplasia of the bone marrow was noted in distant parts of the skeleton and in Cases 3 and 4 in Table I atrophy of the testis was found testified to the dissemination of the radiation effects in the body. This dissemination is strikingly present in the pathology report of our case. In the present case a study of the size of the portal superimposed on an x-ray showing the right kidney shadow indicated that almost the entire right kidney was included in the field of radiation, receiving a full 2,000 r. Paterson[64] and Kunkler and co-workers[65] recognized in their patients, treated for seminoma testis by x-ray bath of the abdominal organs, that when the kidneys received 2,500 r or more, there developed a "new syndrome" eight to twelve months following therapy. This syndrome was characterized clinically by the appearance of weakness and dyspnea, headache, hypertension, edema, albuminuria, azotemia, and a rapidly advancing secondary anemia of a renal type. At times cardiac enlargement and congestive failure were observed. These symptoms were the precursors of severe renal insufficiency and in some cases, death. Paterson[64] concluded that it was not safe to irradiate the entire area of both kidneys to a dose in excess of 2,000 r in

TABLE I. DATA ON DOSAGE, SIZE OF PORTAL AND ELAPSED TIME IN THE CHILDREN REPORTED DEVELOPING NEPHRITIS FOLLOWING EXPOSURE TO ROENTGEN RAYS

CASE	AGE	NEPHREC-TOMY	TOTAL DOSAGE	SIZE OF PORTAL IN CENTI-METERS	DURATION OF LIFE FROM START OF IRRADIATION TO DEATH	DURATION OF LIFE FROM COMPLETION OF IRRADIATION TO DEATH
1 (Domayk)	9 yr.	None	?	?	6 mo.	6 mo.
2 (Zuelzer)	4 yr.	Unilateral	5,850 r	15 × 15	7 mo.	9 wk.
3 (Zuelzer)	3 yr.	Unilateral	5,200 r	15 × 15	6½ mo.	7-8 wk.
4 (Zuelzer)	18 mo.	None	6,850 r	6 × 10	5 mo.	4½ wk.
5 (Grossman)	9 mo.	Unilateral	2,000 r	15 × 20	4½ mo.	3 mo. 28 da.

three- to four-week period. He stated that renal tissue was fundamentally relatively sensitive to the effects of irradiation and that some part of at least one kidney must be preserved free of radiation, or the dose must not exceed 2,000 r. Kunkler and co-workers[65] felt that if a dose of 2,300 r or more was to be delivered to both kidneys the risk of renal failure could best be minimized by ensuring that about one-third of the volume of the kidney be outside the field of irradiation or at least irradiated with as low a dose as possible. They felt that renal function and location should be determined before x-ray treatment of the abdomen was undertaken.

It should be noted that the development of radiation nephritis in Zuelzer's[63] cases followed a very large dose of x-rays (5,200 to 6,850 r). The experience of the Manchester group[64-66] is more in accord with our own, that doses of x-rays of 2,300 r in their cases and 2,000 r in our patient lead to severe renal failure and death.

From the accumulation of clinical reports of the disease entity of radiation nephritis it is felt that careful evaluation of each patient and an increasing concern must be exercised in the use of large doses of irradiation over areas which will include the major portion of both kidneys or the whole of the unilateral kidney following a nephrectomy.

SUMMARY

A review of the literature of irradiation effects on the kidney is presented. A report of a case of radiation nephritis and the subsequent autopsy findings is given. The clinical picture and pathologic characteristics of the disease are pointed out. General consideration of the caution necessary in giving abdominal baths of x-rays is discussed.

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STUDIES OF 17-HYDROXYCORTICOSTEROIDS

IX. The Influence of Therapy on Adrenal Cortical Function in Patients With Rheumatic Fever

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IN RECENT years, hormones (ACTH and cortisone) have been used extensively in the treatment of rheumatic fever. Although a variety of results have been obtained, many investigators feel that hormone therapy is effective in reducing the incidence of residual heart damage as well as in controlling the acute symptomatology in patients with rheumatic fever.[1]

However, considerable concern has been expressed about the possible harmful effects of hormone therapy when administered for periods of weeks or months, particularly when large doses of the drugs are used. Not only is it stated that the side effects produced are annoying and sometimes serious, but also there is speculation about the possibility of producing serious and perhaps permanent alterations in the function of the pituitary-adrenal cortical system.[2, 3, 4] Prolonged cortisone administration is known to suppress the release of ACTH by the pituitary,[5] and in animals to lead to histological changes in the pituitary gland, and to adrenal cortical atrophy.[6] Prolonged ACTH administration has been postulated to produce a refractory state of adrenal cortical function[7] and also possibly to produce irreversible histological alterations in the anterior pituitary gland.[8] Previous evaluation of these potential deleterious effects of long-term hormone therapy in man has been inconclusive, since it has been based only upon clinical observations, including a few necropsy examinations of pituitary and adrenal glands[2] and indirect tests of adrenal cortical function. Such indirect tests are considered less reliable than those which measure directly adrenal cortical secretory activity. The measurement of plasma 17-hydroxycorticosteroid (17-OHCS) concentrations and the response of these concentrations to the injection of ACTH has been proposed as a reliable test of adrenal cortical function.[9] The purpose of this report is to present the results of studies employing this ACTH-17-OHCS response test for evaluation of the influence of prolonged hormone or salicylate therapy on adrenal cortical function in patients with rheumatic fever.

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MATERIALS AND METHODS

The subjects of this study were forty-six children, aged 6 to 15 years,

in whom a diagnosis of active rheumatic fever was established according to the criteria of Jones,[10] with the modifications introduced by Denny and associates.[11] The patients were classified into the following therapy categories: (1) salicylate (six patients), (2) oral cortisone* (fourteen patients), (3) lyophilized ACTH† (eighteen patients), and (4) ACTH gel† (eight patients). Throughout the patients' hospitalization, serial blood specimens were obtained by venipuncture, and the plasmas were frozen until used for determination of 17-OHCS concentrations by the method of Nelson and Samuels.[12] Specimens obtained before institution of therapy are designated as *pre-therapy;* and those obtained within ten days after discontinuing therapy, *post-therapy.* ACTH-17-OHCS response tests[9] were performed on thirty-eight patients during the pre-therapy period, and on nineteen of these patients during the post-therapy period. In two additional patients response tests were performed twelve and twenty-eight days, respectively, after discontinuation of cortisone therapy. Blood specimens for the measurement of 17-OHCS concentrations were obtained just prior to and two hours after the intramuscular injection of 25 I.U. ACTH.

A detailed description of dosage schedules employed in the treatment of these patients has been presented elsewhere.[13] Duration of therapy ranged from 22 to 106 days (mean, 47 days) and the maximum doses employed approximated 1 I.U. per pound per day of ACTH; 2 to 3 mg. per pound per day of cortisone and 60 mg. per pound per day of salicylate.

TABLE I. PRE- AND POST-THERAPY PLASMA 17-OHCS CONCENTRATIONS

THERAPY		NO.	NO.	17-OHCS (μG PER CENT)	P	
CATEGORY	STATUS	PATIENTS	SAMPLES	MEAN ± S.E.M.	PRE VS. POST EACH CATEGOTY	PRE (ALL) VS. POST EACH CATEGORY
Cortisone	Pre	12	25	18.5 ± 2.30	<0.01	<0.01
	Post	8	15	5.4 ± 1.69		
Lyophilized ACTH	Pre	18	35	9.6 ± 1.22	<0.01	<0.01
	Post	16	29	5.3 ± 0.99		
ACTH gel	Pre	8	12	11.3 ± 1.61	>0.1	>0.1
	Post	3	6	7.5 ± 3.21		
Salicylate	Pre	4	6	14.3 ± 3.06	>0.05	<0.01
	Post	6	10	7.2 ± 1.85		
All groups	Pre	42	79	13.0 ± 1.05	<0.01	
	Post*	27	50	5.6 ± 0.84		

*Excludes salicylate group.

OBSERVATIONS

Plasma 17-OHCS Concentrations Pre- and Post-Therapy.—In Table I is shown a comparison of the plasma 17-OHCS concentrations observed in patients during the pre-therapy and post-therapy periods. These observations are categorized according to the drug employed during therapy. It may be observed that there are considerable variations among the pre-therapy mean plasma 17-OHCS values in the differ-

*Cortone supplied through the courtesy of Merck & Co., Inc., Rahway, N. J.

†Acthar and Acthar Gel supplied through the courtesy of the Armour Laboratories, Chicago.

ent groups. Previously it was shown that, as compared with the normal mean values of 12.0 ± 1.29 μg per cent, those children with "well-established" active rheumatic fever (i.e., more than two weeks' duration of rheumatic activity) have abnormally low plasma 17-OHCS concentrations, whereas those with "early acute" rheumatic fever (i.e., less than one week's duration of rheumatic activity) have elevated concentrations of these steroids.[14] Inasmuch as all pre-therapy plasma 17-OHCS values were obtained during one of these two phases of rheumatic activity, a high mean pre-therapy value in a given group reflects a preponderance of patients with "early acute" rheumatic fever and a low mean value a preponderance of patients with "well-established" active rheumatic fever.

In the cortisone-treated group the pre-therapy mean 17-OHCS concentration, reflecting the preponderance of patients with "early acute" rheumatic fever included in this group, was 18.5 ± 2.30 μg per cent. The mean plasma 17-OHCS concentration in this group during the post-therapy period was 5.4 ± 1.69 μg per cent. This value is significantly lower than the pre-therapy value in this group as well as the pre-therapy value of the total hormone group ($p<0.01$).

In the group of patients treated with lyophilized ACTH the mean pre-therapy 17-OHCS concentration was 9.6 ± 1.22 μg per cent. This group consisted primarily of patients with "well-established" active rheumatic fever. Despite this relatively low mean pre-therapy value, the mean post-therapy steroid value of 5.3 ± 0.99 μg per cent was significantly lower ($p<0.01$).

In the group of patients treated with ACTH gel the pre-therapy mean 17-OHCS concentration was 11.3 ± 1.61 μg per cent. The mean post-therapy value was 7.5 ± 3.21 μg per cent which was not significantly lower than the mean pre-therapy value either in this group or in the total hormone-treated group. It should be noted, however, that there were only a few samples obtained during the post-therapy period in this group.

In the group of patients treated with salicylates the mean 17-OHCS level observed during the pre-therapy period was 14.3 ± 3.06 μg per cent. In the post-therapy period the mean value for this group was 7.2 ± 1.85 μg per cent. Although this value is not significantly lower than that found during the pre-therapy period for this group, it is significantly lower than the mean pre-therapy value for all patients.

When all patients were grouped together, a mean pre-therapy steroid value of 13.0 ± 1.05 μg per cent was found. During the post-therapy period a significantly lower mean 17-OHCS concentration, 5.6 ± 0.84 μg per cent, was observed in the total group of hormone-treated patients ($p<0.01$).

ACTH-Steroid Responses.—In order to evaluate the influence that the duration of rheumatic activity might have upon adrenal cortical responsiveness, the ACTH-17 OHCS response tests obtained in the pre-therapy period were grouped according to the duration of illness. Table II shows these data, grouped into three time categories: (1) 1 to 2 weeks, (2) 2 weeks to 6 months, (3) over 6 months. In these three categories the mean plasma steroid responses to ACTH were 26.3

1.84, 19.5 ± 4.06, and 19.4 ± 4.46 μg per cent, respectively. In normal children the mean increase in plasma 17-OHCS following ACTH is 17.8 ± 1.76 μg per cent.[9] Thus it would appear that the duration of the active rheumatic process itself does not influence appreciably adrenal responsiveness to the dose of exogenous ACTH used for these response tests (25 I.U. intramuscularly).

TABLE II. EFFECT OF THE DURATION OF RHEUMATIC ACTIVITY (UNTREATED) ON THE PLASMA 17-OHCS RESPONSE TO ACTH

DURATION OF ACTIVITY	1-2 WK.	2 WK.—6 MO.	>6 MO.
No. patients	8	17	11
Mean 17-OHCS increase ± S.E.M. (μg %)	26.3 ± 1.84	19.5 ± 4.06	19.4 ± 4.46
p value (vs. 1-2 wk. group)	—	>0.1	>0.1

TABLE III. PLASMA 17-OHCS RESPONSE TO ACTH*: PRE- AND POST-THERAPY

	CATEGORY	CORTISONE MEAN ± S.E.M. (μG%)	SALICYLATE MEAN ± S.E.M. (μG%)	ACTH† MEAN ± S.E.M. (μG%)	ALL MEAN ± S.E.M. (μG%)
Pre-Therapy	No. Patients	14	4	20	38
	17-OHCS (μg %)				
	Control	20.3 ± 3.46	9.8 ± 1.91	10.9 ± 1.56	14.3 ± 4.59
	2 hr. post-ACTH	40.0 ± 5.29	32.0 ± 2.58	31.2 ± 5.60	34.3 ± 2.70
	Change	19.7 ± 3.00	22.2 ± 4.56	20.3 ± 3.84	20.0 ± 2.34
Post-Therapy	No. Patients	8	4	7	19
	17-OHCS (μg %)				
	Control	7.4 ± 2.57	6.8 ± 0.88	6.2 ± 2.19	7.8 ± 1.42
	2 hr. post-ACTH	13.8 ± 3.98	14.3 ± 1.60	21.9 ± 4.58	17.8 ± 2.24
	Change	6.4 ± 3.42	7.5 ± 1.19	15.7 ± 5.62	10.0 ± 2.46
	p Value‡	<0.01	<0.05	>0.5	<0.01

*25 I.U. Lyophilized ACTH intramuscularly.

†The ACTH category represents patients receiving either lyophilized ACTH or ACTH gel. Six patients in the pre-therapy period and two patients in the post-therapy period received ACTH gel.

‡p value represents the comparison of the change in 17-OHCS concentration in response to ACTH in the pre-therapy vs. the post-therapy period.

Table III compares the ACTH-17-OHCS responses during the pre-therapy and post-therapy periods in patients of the various therapy categories. In each of the groups during the pre-therapy period the mean increase of plasma 17-OHCS concentrations following ACTH administration was of essentially the same magnitude as that observed in normal children. On the other hand, this response in the post-therapy period was somewhat different. In the group treated with cortisone the plasma 17-OHCS response to ACTH was significantly reduced in the post-therapy period as compared with the pre-therapy period (6.4 ± 3.42 μg per cent vs. 19.7 ± 3.00 μg per cent; $p<0.01$). Although the number of studies in the salicylate group was small, it appears that there was a similar pattern of decreased responsiveness during the post-therapy period in this group. During the post-therapy period in the group of patients treated with lyophilized ACTH or ACTH gel the plasma 17-OHCS response to ACTH (15.7 ± 5.62 μg per cent) was not significantly different from either that during the pre-therapy period (20.3 ± 3.84 μg per cent), or that in normal children (17.8 ± 1.76 μg per cent).

Duration of Adrenal Cortical Suppression Following Cortisone Therapy.—The data in Table III, indicating a suppressive effect of cortisone therapy upon adrenal responsiveness in the immediate post-therapy period, do not provide an evaluation of the duration of this depressed adrenal cortical secretory function. In Fig. 1 the individual ACTH-17-OHCS responses of the eight patients of this group are presented in relation to the time since cessation of therapy. Responses of two additional patients are shown also, one twelve days and the other twenty-eight days after cortisone therapy was discontinued. Of the ten responses, four were within the first four days post-therapy. These show little or no 17-OHCS elevation in response to ACTH, the greatest elevation being 4 μg per cent. There were four responses obtained on the sixth day; one represented a negligible response, one a partial response, and the other two adequate responses. The responses obtained on the twelfth and twenty-eighth days post-therapy also were adequate. Thus, it appears that the depression of steroid response persists for not more than approximately one week after discontinuation of cortisone therapy. The relationship of dose and duration of cortisone therapy to the post-therapy steroid responses of these patients are shown in Table IV. The dose and duration of cortisone administration were individualized and varied considerably from patient to patient. The period of therapy ranged from twenty-three to one hundred seven days, with an average of seven weeks. The total amount of cortisone per patient ranged from 33 to 139 mg. per pound. The average dose of cortisone per day for the entire therapy period ranged from 1.0 to 2.4 mg. per pound. No relationship was observed between length of therapy, daily dose of cortisone, or total dose of cortisone and the magnitude of the ACTH-steroid response. Of the different variable-

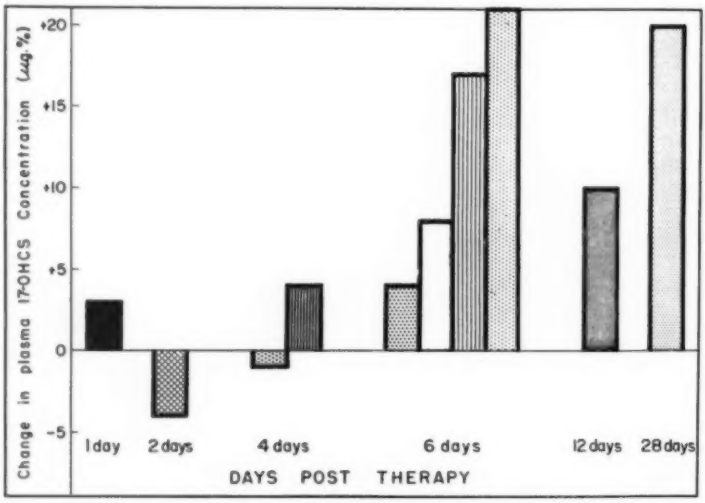

Fig. 1.—Post-therapy plasma 17-hydroxycorticosteroid responses to 25 I.U. ACTH.

considered, only the duration of time following discontinuation of therapy appears to bear a relationship with the adequacy of the steroid response.

DISCUSSION

The majority of the patients in this study received approximately 1 I.U. per pound per day ACTH or 2 to 3 mg. per pound per day cortisone for several weeks. To assess the effect of this therapy on adrenal cortical function in these patients, measurements of the plasma 17-OHCS concentrations and the response of these concentrations following ACTH stimulation were performed during the pre- and post-therapy periods. In interpreting the data concerning the differences between plasma 17-OHCS concentrations in these periods it should be remembered that at least two factors may be operative in producing the low plasma 17-OHCS concentrations during the post-therapy period: (1) the suppressive effect on adrenal cortical function of prolonged hormone therapy and (2) the natural course of the disease. With regard to the latter, it has been shown that patients in the "early acute" phase of rheumatic fever have elevated plasma steroid levels, whereas in all other phases of the disease they have abnormally low levels.[14] During the pre-therapy period many of these patients were in the stage of "early acute" rheumatic fever, whereas none of them could be so classified during the post-therapy period. Therefore, some decrease in plasma 17-OHCS concentrations would be expected in the post-therapy period on this basis. The post-therapy plasma 17-OHCS concentration (5.6 ± 0.84 μg per cent) of the total group in this study is not different from the concentration (5.9 ± 0.93 μg per cent) reported[14] for untreated, "well-established," active rheumatic fever patients. Therefore, the decreased plasma 17-OHCS levels in the post-therapy period cannot be interpreted justifiably as reflecting a suppressive effect of therapy on adrenal cortical function.

However, the decreased responsiveness of the adrenal gland, as manifested by the decreased plasma 17-OHCS response to ACTH, observed during the post-therapy period in the cortisone and salicylate treated groups, cannot be attributed to the natural course of the disease. That this decreased responsiveness is not a reflection of the natural pattern of the disease process is demonstrated by the results of steroid response test in untreated patients

TABLE IV. RELATIONSHIP OF CORTISONE DOSE, DURATION OF CORTISONE THERAPY, AND POST-THERAPY DAY TO THE ACTH-17-OHCS RESPONSE

		CORTISONE			PLASMA 17-OHCS RESPONSE (μG%)			
NO.	PATIENT	DAYS OF THERAPY	MG./LB. TOTAL	MG./LB./ DAY AVERAGE	DAY POST-THERAPY	0 HR.	2 HR.	CHANGE
1.	T. L.	41	96	2.3	1	0	3	+ 3
2.	W. K.	33	33	1.0	2	17	13	− 4
3.	S. B.	28	34	1.2	4	16	20	+ 4
4.	T. F.	42	61	1.5	4	4	3	− 1
5.	J. B.	55	54	1.0	6	1	5	+ 4
6.	C. R.	52	68	1.3	6	6	14	+ 8
7.	L. A.	52	125	2.4	6	6	23	+17
8.	K. C.	23	42	1.8	6	8	29	+21
9.	B. R.	54	119	2.2	12	10	20	+10
10.	F. A.	103	139	1.3	28	6	26	+20

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with active rheumatic fever of varying duration (Table II). In these untreated patients, even when rheumatic activity had been present for six months or more, the mean steroid response was not statistically different from that during the first two weeks of illness or from that in normal children. Therefore, a decreased responsiveness in the post-therapy period probably is attributable to the influence of the therapy administered. The decreased response in the post-therapy period in the cortisone-treated patients might well be explained by the action of cortisone in suppressing pituitary ACTH release with consequent functional and morphological changes[2] in the adrenal cortex.

However, this suppressive effect of cortisone upon adrenal cortical secretory activity apparently is quite temporary. From the data shown (Fig. 1) it appears that adrenal function remains suppressed for not longer than one week following cortisone therapy. Similar findings were reported by Eik-Nes and associates[15] concerning the plasma 17-OHCS response to intravenous ACTH in two patients during the period immediately after cortisone therapy. Moreover, on the basis of the ten patients studied here in the post-cortisone therapy period, there is no evidence to suggest that the amount of cortisone used or the duration of therapy exerts any significant effect in prolonging this suppressive effect.

These findings do not appear to be in conformity with the observations in man[16] and animals[17] of adrenal atrophy following prolonged administration of cortisone. One might infer that secretory function and morphological change need not be associated. Because the adrenal atrophy following prolonged cortisone therapy in animals can be prevented by concurrent ACTH administration,[18] the combined use of ACTH and adrenal cortical steroids has been suggested to prevent adrenal hypofunction. However, the depression of adrenal function following therapy with cortisone alone seems to be so transitory that combination ACTH and steroid therapy would hardly seem indicated for this purpose.

An obvious explanation is not available for the decreased adrenal responsiveness in the post-therapy period in the patients treated with salicylates. A detailed discussion of data from this laboratory pertaining to the relationship between salicylates and adrenal cortical function will be presented elsewhere.

Among the patients treated with ACTH, that group which received lyophylized ACTH had low post-therapy steroid values similar to those in the cortisone and salicylate groups, whereas the group treated with ACTH gel showed no decreased steroid values in the post-therapy period. A possible explanation for this difference may be continued stimulation of the adrenal cortex after discontinuation of therapy due to accumulation of ACTH gel in multiple depot sites. It is interesting to note that in the ACTH-treated group there was no significant decrease in the responsivenes of the adrenal cortex to ACTH stimulation during the post-therapy period. This would indicate that ACTH, administered in the dosage and for the duration of time used in this study, does not cause so-called "adrenal exhaustion."

SUMMARY

1. Data are presented concerning plasma 17-OHCS concentrations and the responses of these concentration-

to ACTH in patients with rheumatic fever during the periods before and after hormone or salicylate therapy.

2. In all therapy groups, except the one treated with ACTH gel, the mean plasma 17-OHCS level was significantly lower during the post-therapy period than during the pre-therapy period, but not significantly lower than in untreated patients with active rheumatic fever of the same duration.

3. In all therapy groups, the 17-OHCS responses to intramuscular ACTH were normal during the pre-therapy period. During the post-therapy period the magnitude of this response was reduced significantly in the cortisone- and the salicylate-treated groups but not in the ACTH-treated groups.

4. The data presented are interpreted as indicating that a relative and temporary suppression of adrenal cortical responsiveness occurs following therapy with cortisone; this suppressive effect apparently persists for not more than one week. Within the range of size of dose and duration of therapy employed neither of these variables appeared to influence directly the adrenal hypofunction in the post-therapy period.

5. In the patients treated with salicylates, there appeared to be a decreased adrenal cortical responsiveness in the post-therapy period.

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OXYGEN THERAPY IN THE NEWBORN PREMATURE INFANT

I. Its Relation to Some Aspects of Protein Metabolism

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IT HAS been established by Smith and associates[1] and Gaisford and Schofield[2] that fasting and thirsting of newborn premature infants provide definite clinical advantages and benefits resulting in a decrease in morbidity and possibly a lowering of mortality rates. This is accomplished, at least in part, through a reduction of the water-logged state in which many premature infants have been found at birth. The use of oxygen therapy in these newborn patients has long been accepted as prophylactic and supportive care of the finest quality. Recently, however, suspicion has been directed toward oxygen as a possible cause of retrolental fibroplasia. The immediate effect has been to deter the zest for widespread use of this agent, particularly in the case of the extremely small infant and with respect to very high concentrations.

Sometime ago, while initiating a study of general metabolic effects consequent to fasting and thirsting premature infants, it was deemed advisable to ascertain whether the withholding of supplementary oxygen from the incubator would cause adverse changes clinically or otherwise. The results of these studies with respect to selective electrolytes have been reported elsewhere.[3] The present report will describe observations which relate changes in certain aspects of protein metabolism to the presence or absence of extra oxygen in the environment of premature infants.

METHODS AND PROCEDURES

Eighty-three premature infants born in Hubbard Hospital, and varying in weight from 1,525 to 2,490 grams, comprise the sample for study. Upon admission to the nursery, infants were placed in Gordon-Armstrong or Isolette incubators and were exposed either to unfortified incubator air or to 2 to 4 liters (24 to 34 per cent)* of oxygen per minute. Some few received 6 liters (38 to 42 per cent)* per minute. Infants were assigned to oxygen-enriched incubators and to those containing ordinary room air on an alternate basis. The two groups were comparable in other respects. All

From Meharry Medical College.

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*Determinations for oxygen concentration were made with an O.E.M. oxygen analyzer supplied commercially by the Oxygen Equipment Mfg. Corp., East Norwalk, Conn. No difference was observed in blood chemical composition with the use of 40 per cent concentrations of incubator oxygen as compared with 30 per cent concentrations.

infants were fasted and thirsted for periods of time varying from 12 to 96 hours in duration. Adverse clinical signs indicating significant dyspnea, cyanosis, looseness of stools, etc., were used as criteria for exclusion from the study. Blood samples were drawn for analysis from the femoral vein on the day of birth, and on the third, fifth, seventh, and fourteenth days of life. Heparin was used as the anticoagulant, and, following collection, samples were immediately centrifuged and placed in a freezer until analyzed. Upon removal from the freezer, plasma samples and blood filtrates were allowed to attain room temperature before analysis. Chemical determinations were made for total plasma proteins, nonprotein nitrogen, urea nitrogen, and uric acid. For nonprotein nitrogen,[4] 4 ml. of 1:10 Folin-Wu tungstic acid filtrate was digested with 1 ml. of 50 per cent H_2SO_4, and the Kjeldahl digest steam distilled into 25 ml. of 2 per cent boric acid solution and titrated with 0.01N HCl, using a mixed indicator of bromeresol green and methyl red. For total plasma proteins a similar procedure was used, except that 1 ml. of plasma diluted 1:3 and 1 ml. of concentrated H_2SO_4 were used for the Kjeldahl digest. A mixture of $CuSO_4$ and K_2SO_4 was used as catalyst.

Uric acid was determined by the method of Brown.[5] Two milliliters of 1:10 tungstic acid filtrate was treated directly with 1 ml. of a special uric acid reagent in the presence of 4 ml. of cyanide-urea solution (50 per cent of each reagent) and the color developed compared with that of a uric acid standard treated in similar manner in a Klett-Summerson photoelectric colorimeter. The Method of Gentzkow and Masen[6] was used for blood urea nitrogen. Five milliliters of whole heparinized blood was added to 35 ml. of distilled water and the urea nitrogen liberated by the action of urease power. The solution was then deproteinized with tungstic acid and filtered. Five milliliters of the filtrate was treated with 4 ml. of a special reagent, including a gluconate, a persulfate, and Nessler's reagent (1 gluconate + 1 persulfate + 2 Nessler's reagent) and the color developed compared with a standard treated similarly. Filter No. 54 was used.

RELATION OF WEIGHT CHANGES TO OXYGEN THERAPY

For the purpose of studying possible effects of supplementary oxygen on weight changes following birth, sixty-two cases were divided into two groups according to birth weight. Group I included those infants weighing 2,000 grams or less, while Group II comprised those above 2,000 grams. These groups were further subdivided according to duration of fasting,* and finally were compared with respect to presence or absence of supplementary incubator oxygen.

The data in Table I show that in every case infants exposed to extra oxygen averaged a somewhat greater percentage weight loss than those breathing unfortified incubator air.

It is moreover observed that, in general, the per cent of weight loss was greater in the smaller infants, and of course in those fasted and thirsted for longer periods of time.

*In all infants, fasting was complete and therefore embraced thirsting.

TABLE I. AVERAGE CHANGES IN WEIGHT FOLLOWING BIRTH IN PREMATURE INFANTS FASTED FOR VARYING PERIODS WITH AND WITHOUT SUPPLEMENTARY OXYGEN

GROUP	NUMBER OF CASES	SUPPLEMENTARY OXYGEN	FASTING PERIOD (HOURS)	BIRTH WEIGHT (GRAMS)	MAXIMUM WEIGHT LOSS (3RD-5TH DAY)	
					GRAMS	PER CENT
I*	6	Yes	48	1,786	230	12.9
II*	7	No	48	2,329	196	8.4
II	5	Yes	48	2,305	252	10.9
I	4	No	72	1,795	218	12.1
I	14	Yes	72	1,796	248	13.8
II	3	No	72	2,322	298	12.8
II	7	Yes	72	2,178	295	13.5
I	6	No	96	1,732	300	17.3
I	1	Yes	96	1,675	350	20.9
II	6	No	96	2,213	325	14.7
II	3	Yes	96	2,342	400	17.1

*Group I—2,000 grams or less; Group II—above 2,000 grams.

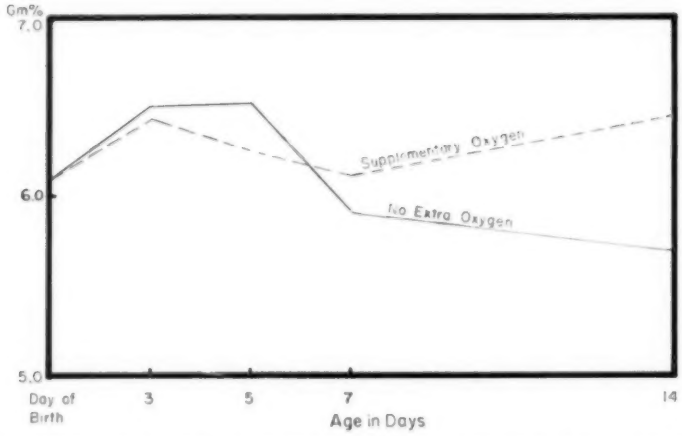

Fig. 1.—Comparison of total plasma protein values in premature infants fasted 72 and 96 hours with and without supplementary oxygen.

TABLE II. MEAN PLASMA PROTEIN VALUES IN PREMATURE INFANTS FASTED FOR VARYING PERIODS WITH AND WITHOUT SUPPLEMENTARY OXYGEN

AGE IN DAYS	FASTING PERIOD IN HOURS	TOTAL NO. OF CASES	SUPPLEMENTARY OXYGEN		NO EXTRA OXYGEN	
			PLASMA PROTEIN GRAMS %	NO. OF CASES	PLASMA PROTEIN GRAMS %	NO. OF CASES
Day of birth	--	25	6.09	--	6.09	--
3	72	19	6.39	15	6.28	4
	96	8	6.60	3	6.68	5
5	72	19	6.22	17	5.95	2
	96	7	6.40	2	6.74	5
7	72	18	6.07	15	5.50	3
	96	8	6.30	3	6.16	5
14	72	14	6.45	12	5.30	2
	96	4	6.40	1	5.90	3

PLASMA PROTEINS

Data available from twenty-seven cases reveal a mean plasma protein value, on the day of birth, of 6.09 grams per cent.

There was an immediate but slight rise during the first few days of life, presumably indicative of dehydration, and this can be correlated somewhat with duration of fasting. During the first week of life, supplementary oxygen had no effect on plasma protein concentration. However, it is noted later that from age 7 to 14 days the mean plasma protein level is approximately 0.8 gram per cent lower in infants breathing unfortified incubator air (Fig. 1).

Smith[7] points out that the usual level of total serum or plasma protein during the newborn period is about 1 gram per 100 ml. less than in the adult, and averages from 6 to 7 grams per cent. Total protein concentration is even lower in premature infants (4.5 to 5.5 grams per cent). The somewhat higher mean values found in the present study cannot be explained fully on a basis of dehydration, birth weight, nor with respect to the presence or absence of edema. Protein values range from 4.5 to 8.7 grams per cent in edematous infants weighing approximately 1,600 grams. The fact that this irregular pattern occurred frequently in other weight groups clearly demonstrates the lack of correlation between weight at birth and total plasma protein concentration.

TABLE III. MEAN BLOOD NONPROTEIN NITROGEN VALUES IN PREMATURE INFANTS FASTED FOR VARYING PERIODS WITH AND WITHOUT SUPPLEMENTARY OXYGEN

AGE IN DAYS	FASTING PERIOD IN HOURS	TOTAL NO. OF CASES	SUPPLEMENTARY OXYGEN		NO EXTRA OXYGEN	
			NPN (MG. %)	NO. OF CASES	NPN (MG. %)	NO. OF CASES
Day of birth	--	83	39.86	--	39.86	--
3	12 and 24*	13	39.81	13	--	--
	48	18	48.22	11	37.80	7
	72	34	56.64	27	43.22	7
	96	12	58.52	5	44.02	7
	Total cases	77		56		21
5	12 and 24*	12	44.87	12	--	--
	48	17	46.48	10	40.05	7
	72	37	56.69	31	41.13	6
	96	13	63.84	5	39.76	8
	Total cases	79		58		21
7	48	2	--	--	60.85	2
	72	22	65.56	19	45.12	5
	96	8	61.60	3	51.24	5
	Total cases	32		22		12
14	72	15	65.12	12	62.83	3
	96	4	73.50	1	42.23	3
	Total cases	19		13		6

*The data from these two groups were combined.

BLOOD NONPROTEIN NITROGEN

The data from eighty-three cases are available for consideration, and inspection of Table III reveals the effect of fasting and thirsting on the level of blood nonprotein nitrogen. A mean value of 39.86 mg. per cent was observed on the day of birth. If the infant receiving supplementary incubator oxygen is fed during the

first 12 to 24 hours, no change is noted in the nonprotein nitrogen when determinations are made on the third day of life. If, however, he is fasted and thirsted for 48 hours during this period, there is an average rise by about 8 mg. per cent, and when he is starved* for 72 or 96 hours the increase in NPN is more than double this value. It is observed that, on the third day of life, infants fasted 96 and 72 hours, with supplementary oxygen, is, respectively, four and one-half and five times greater than in infants breathing incubator air. The same phenomenon is repeated in varying degree throughout.

Fig. 2 reveals the persistent elevation of NPN in infants given supplementary oxygen, with a gradual

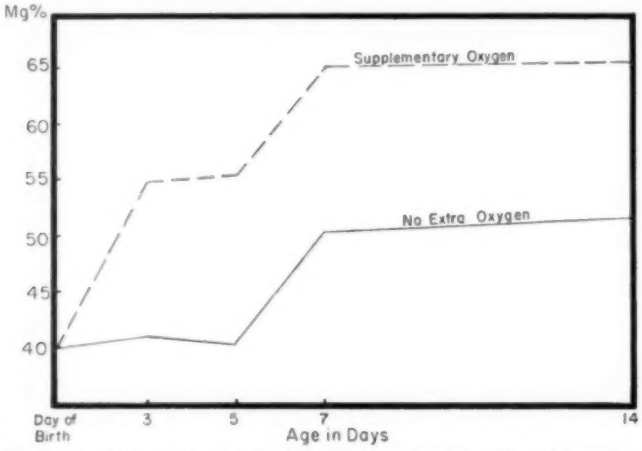

Fig. 2.—Blood nonprotein nitrogen in fasted premature infants with and without supplementary incubator oxygen.

TABLE IV. RELATION OF BIRTH WEIGHT TO BLOOD NONPROTEIN NITROGEN IN PREMATURE INFANTS FASTED FOR VARYING PERIODS WITH AND WITHOUT SUPPLEMENTARY OXYGEN

NUMBER OF CASES	DURATION OF FASTING IN HOURS	SUPPLEMENTARY OXYGEN	AVERAGE BIRTH WEIGHT IN GRAMS	NPN (MG. %) ACCORDING TO AGE IN DAYS				
				DAY OF BIRTH	3	5	7	14
7	48	No	2,329		37.8	40.1	60.9	--
5	48	Yes	2,305		55.5	42.0	--	--
4	72	No	1,795	Average	40.1	45.5	51.2	62.8
14	72	Yes	1,796	39.86	54.0	62.5	65.1	70.4
3	72	No	2,310		47.4	36.8	20.7	--
7	72	Yes	2,178		55.9	61.8	66.1	54.7

not only was there no rise in the level of the NPN in those infants who were fasted 48 hours and who received no extra incubator oxygen, but there was a slight decline. Moreover, the third-day rise in those infants fasted 96 and 72 hours, with supplementary oxygen, is, respectively, four and one-half and five times greater than in infants breathing incubator air. The same phenomenon is repeated in varying degree throughout.

Fig. 2 reveals the persistent elevation of NPN in infants given supplementary oxygen, with a gradual increase from the third through the fourteenth day of life, while at the same time it demonstrates in striking contrast the more or less fixed level from birth through the fifth day when extra incubator oxygen was withheld.

*Fasted and thirsted.

Table IV indicates clearly that differences in birth weight have no influence on fluctuations in the level of the blood nonprotein nitrogen due to the presence or absence of supplementary incubator oxygen.

BLOOD UREA NITROGEN

Similarity of the blood urea nitrogen pattern with that of the NPN is revealed in Figs. 2 and 3.

The presence of supplementary oxygen, in those infants fasted three

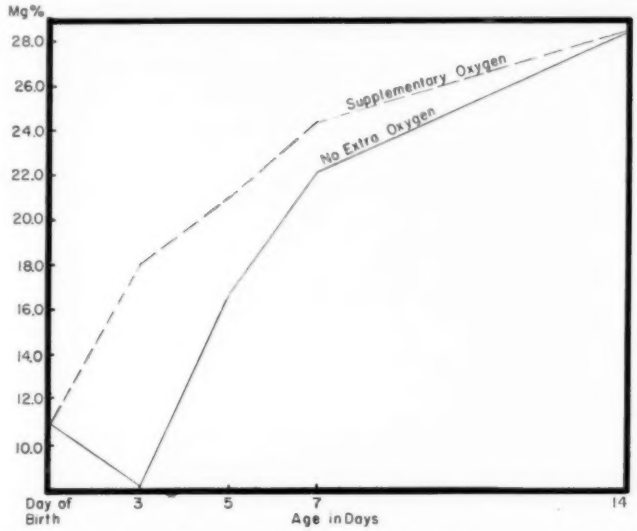

Fig. 3.—Blood urea nitrogen in premature infants fasted 72 hours with and without supplementary oxygen.

TABLE V. MEAN BLOOD UREA NITROGEN IN PREMATURE INFANTS FASTED FOR 72 HOURS WITH AND WITHOUT SUPPLEMENTARY OXYGEN

AGE IN DAYS	TOTAL NUMBER OF CASES	SUPPLEMENTARY OXYGEN		NO EXTRA OXYGEN	
		BUN (MG. %)	NO. OF CASES	BUN (MG. %)	NO. OF CASES
Day of birth	26	10.82	--	10.82	--
3	25	17.95	21	8.10	4
5	26	20.89	21	16.68	5
7	25	24.37	20	22.10	5
14	22	28.44	18	28.42	4

Blood nonprotein nitrogen tends to rise during the first days of life, even if feeding is begun on the day of birth (Table III). Fasting and thirsting superimpose an additional rise consequent to hydropenia, and in the present study the exposure to supplementary incubator oxygen elicits a final augmentation in NPN concentration.

days or more, is associated with a progressive rise in both NPN and BUN, while those exposed only to incubator air show little or no rise during the first three days of life.

Determinations made for blood urea nitrogen concentration on twenty-six infants revealed a mean value of 10.8 mg. per cent on the day of birth. On the third day of life,

the blood urea nitrogen of those infants receiving extra oxygen had risen by more than 7 mg. per cent, while the mean value in babies exposed to unfortified incubator air showed a slight fall (2.82 mg. per cent). The data in Table V reveal that, at every period, the BUN values were higher in those infants exposed to supplementary oxygen.

BLOOD URIC ACID

Blood uric acid determinations were completed on thirty-four infants. The mean value at birth was 7.09 mg. per cent.

During the first three days of life there was a slight rise, but following this there ensued a precipitous fall which was greater in those infants not receiving supplementary oxygen (Fig. 4).

The fall in uric acid concentration between the fifth and seventh days was associated with a corresponding fall in plasma protein, and a concomitant rise in blood urea and non-protein nitrogen.

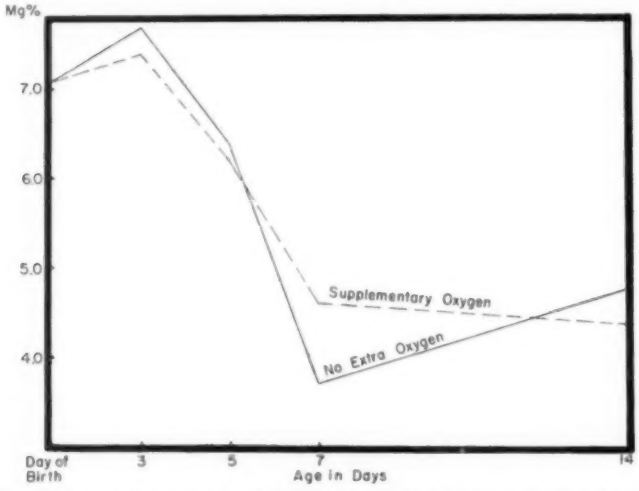

Fig. 4.—Comparison of blood uric acid in fasted premature infants with and without supplementary oxygen.

TABLE VI. MEAN BLOOD URIC ACID VALUES IN PREMATURE INFANTS FASTED FOR 72 AND 96 HOURS WITH AND WITHOUT SUPPLEMENTARY OXYGEN

AGE IN DAYS	FASTING PERIOD IN HOURS	TOTAL NO. OF CASES	SUPPLEMENTARY OXYGEN		NO EXTRA OXYGEN	
			URIC ACID (MG. %)	NO. OF CASES	URIC ACID (MG. %)	NO. OF CASES
Day of birth	--	34	7.09	--	7.00	--
3	72	24	7.51	19	7.82	5
	96	7	7.00	3	7.60	4
5	72	22	5.83	18	7.35	4
	96	7	8.57	3	5.45	4
7	72	21	4.81	16	4.00	5
	96	7	2.95	2	3.40	5
14	72	16	4.56	13	5.40	3
	96	4	1.90	1	4.10	3

SUMMARY AND CONCLUSIONS

The effects of fasting and thirsting upon a total of eighty-three newborn premature infants with and without supplementary incubator oxygen were studied with respect to certain aspects of protein metabolism. It was observed that exposure to extra incubator oxygen was associated with a somewhat greater percentage of weight loss following birth than occurred when infants breathed ordinary incubator air. No significant difference was noted in total plasma protein concentration during the first seven days of life when oxygenated and unoxygenated babies were compared. Following this, however, a progressive dissociation occurred which resulted in mean values of 6.45 gm. per cent for the former and 5.66 gm. per cent for the latter on the fourteenth day.

Changes in the blood nonprotein nitrogen concentration were striking. When infants were exposed to supplementary oxygen, the NPN content promptly increased, whereas no significant change was noted in those breathing unfortified air during the first five days of life. Throughout the period of study, the NPN concentration in oxygenated infants remained at a level of from 12 to 15 mg. per cent above that of controls who received no extra oxygen. A similar dissociation was noted with respect to blood urea during the first three days of life. Blood uric acid concentrations were closely parallel during the period of study.

The implications of the findings in this study are not clear, and further study is anticipated. Whether oxygen administration in some way enhances the utilization of body tissue in fasting premature infants remains to be demonstrated.

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A COMPARISON OF INTRAMUSCULAR BENZATHINE PENICILLIN AND ORAL SULFONAMIDE IN THE CONTROL OF RHEUMATIC RECURRENCES

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THE crucial role of the Group A streptococcus in the causation of rheumatic fever is generally admitted by most authorities. This notion has been supported by the results of antimicrobial therapy in two types of investigation: (1) reduction of rheumatic fever incidence following mass treatment of streptococcal infections; (2) reduction of rheumatic fever recurrences during continuous prophylaxis in individuals who have already suffered one or more episodes.[1]

The Richmond Clinic of the Virginia State Rheumatic Fever Program has been studying the characteristics of rheumatic fever in Virginia since 1940. A preliminary report in 1948[2] described the nature of our patient population and the diagnostic criteria utilized in classification. A recurrence rate of 61 per cent in a group of 225 cases followed for three years was observed. A second communication in 1952[3] reported the results of continuous sulfonamide prophylaxis in 190 cases followed for an average of forty-four months. A recurrence rate of 2.9 per cent was seen during an average period of twenty-four months with sulfadiazine and 1.5 per cent during an average of eleven months with sulfisoxazole (Gantrisin).

From the Departments of Pediatrics and Medicine, Medical College of Virginia, and the Richmond Clinic of Virginia State Rheumatic Fever Program.

Benzathine penicillin* (N-N'dibenzylethylenediamine penicillin) is an ester of penicillin G[4] with a differing pharmacodynamic action depending on its route of administration. An oral dose of 200,000 to 400,000 units is taken daily for continuous prophylaxis. When 1,200,000 units of the drug is injected intramuscularly, measurable blood levels can be detected up to twenty-eight days subsequently. This remarkably prolonged repository action is presumably due to the slow release of active penicillin from the depot.

Reports on the use of benzathine penicillin intramuscularly for prophylaxis against rheumatic recurrence are few at present. The available data are summarized in Table I, including our own results.

PURPOSE

It is now recognized that any patient who has had acute rheumatic fever should have some type of prophylactic medication for an indefinite period of time. The primary purpose of this project was to study recurrences of rheumatic fever as influenced by two drugs. The plan was to observe over a two-year period the influence of monthly intramuscular injections of benzathine penicillin G on rheumatic recurrences. A series of patients on sulfonamides served as controls.

*Supplied by Wyeth Laboratories, Philadelphia, Pa.

MATERIAL

Fifty patients were selected from the convalescent wards and outpatient department of the Richmond Rheumatic Fever Clinic in the fall of 1952 for benzathine therapy. All of this group had recently experienced rheumatic fever and were in the age group and stage of the disease where some type of prophylaxis was clearly indicated. They were of necessity in the hospital or in the area served by Richmond so that visits to the clinic every twenty-eight days for intramuscular injections were feasible. Many had such a background that reliable oral dosage was impossible. Seven had a leukopenia on a sulfonamide, requiring its cessation. The ages at onset of prophylaxis, race, sex, and cardiac diagnoses are listed in Table II. There were twenty-two males and twenty-four females, twenty of whom were white and twenty-six Negro. Four patients dropped out.

Fifty comparable cases were chosen and maintained on sulfonamide prophylaxis. The same criteria for diagnosis and same general care were given to both groups. As will be noted from Table III, part of this group was on sulfadiazine and part on Gantrisin, but it was not felt that this made any significant difference. Of these, twenty-four were males and twenty-two females with thirty-one white and 15 Negro. Again four cases failed to follow through.

While every attempt was made to start patients on prophylaxis as soon as possible, many of the benzathine penicillin group had previously tried other drugs. The most irresponsible of the group were shifted to this program. Other new cases were started on it promptly. The average age when prophylaxis was started was 10.2 years. The mean months since the onset of the last attack were 12.

In the sulfonamide controls, many were started in the late 1940's. The usual procedure was to wait until the patient was considered inactive before sulfa was begun. Often the initial episode was a long one. The average age at onset of prophylactic therapy was 11 years with a mean of 9 months since the beginning of the last attack (see Table IV).

TABLE I. INTRAMUSCULAR BENZATHINE PENICILLIN PROPHYLAXIS OF RHEUMATIC RECURRENCE

INVESTIGATOR	NO. OF INJECTIONS	NO. OF PATIENTS	AVERAGE ½ PERIOD (MO.)	PATIENT MONTHS	RHEUMATIC RECURRENCES	ALLERGIC REACTIONS
Stollerman, G. H., and associates[5]	2,631	285	10	2,841	0	7
Diehl, A. M., and associates[6]	962	96	14	1,344	0	2
Perry, C. B., and Gillespie, W. A.[7]	64	22	3		1	0
McCue, C. M., and associates	1,103	46	24	1,104	0	1
Totals	4,760	449		5,289	1	10

The criteria for diagnosis in the benzathine group and sulfa group were as follows:

	Benzathine Penicillin	*Sulfonamides*
Carditis and polyarthritis	32	31
Carditis alone	5	4
Polyarthritis alone	6	8
Polyarthritis and chorea	1	1
Carditis and chorea	2	2

TABLE II. CASE STUDY: BENZATHINE PENICILLIN GROUP

NO.	AGE PROPHY-LAXIS STARTED	RACE AND SEX	MONTHS SINCE ONSET LAST ATTACK R.F.	CARDIAC DIAGNOSIS	BICILLIN SHOTS NO.	REMARKS
1	3	WM	13	M.I.	12	Moved to North Carolina, 3/54
2	14	NF	24	M.I. C.E.	28	2 attacks prior to Bicillin
3	6	NM	8	C.E. Myo.	26	
4	14	NF	24	M.I. M.S. C.E.	25	2 attacks prior to Bicillin
5	12	WM	2	No H.D.	24	
6	13	WM	14	No H.D.	26	
7	4	NF	3	C.E. Myo.	21	
8	11	NM	9	M.I. M.S. C.E. Failure	27	2 attacks prior to Bicillin S.B.E. in 1951 Nephritis in 1952 Failure in 1952 *Failure in 1954
9	15	WF	6	M.I. C.E. M.S. A.I.	25	3 attacks prior to Bicillin
10	12	WM	50	M.I.	26	3 attacks prior to Bicillin
11	7	WF	12	Myo.	25	Legg-Perthes disease in 1953 Anemia in 1953 Sister developed R.F.
12	16	WM	5	Myo.	19	Entered Navy, 5/54
13	13	WF	13	No. H.D.	20	
14	10	WF	8	M.I.	28	Repeated polyarthritis. No unknown in past
15	10	NF	15	M.I. C.E.	21	2 attacks prior to Bicillin
16	14	WM	48	M.I.	23	2 attacks prior to Bicillin
17	6	NF	9	M.I. M.S. C.E. A.I.	26	
18	7	NF	9	M.I.	25	Sister and cousin died with R.F.
19	10	WM	36	M.I. C.E.	26	2 attacks prior to Bicillin
20	9	NF	3	M.I. C.E.	25	
21	5	NF	2	C.E.	25	
22	5	WF	1	M.I. C.E.	20	? Attack, aged 4
23	11	NM	12	M.I. M.S. C.E. Failure	28	Severe lung, first attack
24	12	NM	36	M.I.	23	2 attacks prior to Bicillin Nephrotic stage of glomerulo nephritis in 1951-1952

Key:

M.I.	Mitral insufficiency.	Myo.	Myocarditis.
M.S.	Mitral stenosis.	H.D.	Heart disease.
A.I.	Aortic insufficiency.	S.B.E.	Subacute bacterial endocarditis.
A.S.	Aortic stenosis.	R.F.	Rheumatic fever.
C.E.	Cardiac enlargement.	I.A.S.D.	Interatrial septal defect.

TABLE II.—CONT'D

NO.	AGE PROPHY-LAXIS STARTED	RACE AND SEX	MONTHS SINCE ONSET LAST ATTACK R.F.	CARDIAC DIAGNOSIS	BICILLIN SHOTS NO.	REMARKS
25	10	WM	29	A.I. A.S. M.I. M.S. C.E.	27	3 attacks prior to Bicillin Failure and pericarditis in 1949-1951
26	9	NM	16	M.I. M.S. C.E.	27	2 attacks prior to Bicillin S.B.E. in 1951
27	6	WM	3	M.I. C.E. A.S.	23	
28	8	NF	3	M.I.	25	
29	8	NM	29	No H.D.	28	
30	13	NF	15	M.I. M.S. A.S. C.E. Failure Fibrillation	27	*See text Chronic R.H.D. active since June, 1951
31	14	NF	13	M.I. M.S. C.E.	25	4 attacks prior to Bicillin Severe social problems
32	15	NM	40	M.I.	26	
33	12	NM	8	M.I. C.E. Myo.	26	
34	13	WF	30	M.I. M.S.	23	Would not take oral prophylaxis Anemia now
35	11	WM	18	M.I.	16	Mentally retarded Chronic mastoiditis
36	4	NF	8	C.E.	22	Severe bronchitis, 3/54
37	12	NM	10	C.E. M.I. A.I. Pericar-ditis Failure	21	3 attacks prior to Bicillin with pericarditis
38	12	NF	6	M.I.	26	2 attacks prior to Bicillin
39	11	NF	24	M.I. C.E.	26	
40	14	NM	<1	No H.D.	17	
41	9	WF	6	No H.D.	25	2 attacks prior to Bicillin
42	16	NM	60	M.I. M.S. A.I. C.E.	27	Active disease over 2 years
43	11	WF	48	C.E. Myo. (Nodules)	23	Active disease 3-plus years
44	12	NF	12	C.E. M.I.	25	
45	6	WF	7	C.E. (Rash)	25	Mother developed active R.F. in 1954
46	6	WM	5	No H.D.	19	

*Case discussed in text under "Results."

TABLE III. CASE STUDY: SULFONAMIDE GROUP*

NO.	AGE PROPHYLAXIS STARTED	RACE AND SEX	MONTHS SINCE ONSET LAST ATTACK R.F.	CARDIAC DIAGNOSIS	MONTHS DURATION THERAPY	RECURRENCES ON SULFA	REMARKS
1	16	WM	8	M.I.	24		Sulfadiazine
2	14	NF	5	M.I.	40		Sulfadiazine Sister had R.F. in 1944 2 attacks prior to sulfadiazine
3	9	NM	4	M.I. M.S. A.I. A.S. C.E.	16		Sulfadiazine
4	14	WM	13	M.I. C.E.	46		Gantrisin and sulfadiazine
5	17	WM	6	Myo. M.I. M.S. C.E. A.I.	60		7 attacks prior to sulfadiazine
6	17	NF	24	M.I. M.S. A.I. C.E. Myo.	24		Sulfadiazine 2 attacks prior to sulfadiazine
7	19	WM	19	A.I. A.S. M.I. M.S. C.E.	47		Gantrisin
8	12	NF	33	M.I. M.S. I.A.S.D. Failure	69		Sulfadiazine First attack, duration over 2 yr.
9	8	WM	7	M.I. M.S. C.E. Myo. Failure	53		Gantrisin
10	16	WM	5	M.I.	23		Sulfadiazine
11	13	NF	13	M.I.	33		Gantrisin
12	4	WF	7	No H.D.	4		Sulfadiazine Father had R.F.
13	15	WF	6	M.I.	7		Sulfadiazine
14	10	WF	8	No H.D.	24	1 attack 2/54	Sulfadiazine
15	8	WM	6	No H.D.	30	1 attack 2/53	2 attacks prior to sulfadiazine
16	11	NF	12	A.I. M.I. M.S. C.E.	15	? Attack 4/53	Gantrisin 2 attacks prior to Gantrisin
17	9	WM	8	No H.D.	26		Sulfadiazine
18	7	WM	8	No. H.D.	68		3 attacks prior to sulfadiazine Brother had R.F.
19	15	WF	12	A.I. M.I.	27	? Attack 9/53	3 attacks prior to sulfadiazine Chorea
20	14	WM	3	Pericarditis M.I.	24		2 attacks prior to sulfadiazine

*For key to abbreviations, see Table II.

TABLE III. CONT'D

NO.	AGE PROPHYLAXIS STARTED	RACE AND SEX	MONTHS SINCE ONSET LAST ATTACK R.F.	CARDIAC DIAGNOSIS	MONTHS DURATION THERAPY	RECURRENCES ON SULFA	REMARKS
21	16	WM	8	No H.D.	36		Mother had R.F. Chorea in 3 attacks prior to Gantrisin Chronic otitis media
22	13	NF	18	M.I. A.I. A.S. C.E.	44		Gantrisin Delivered normal infant, 1953
23	7	WM	10	No H.D.	81		3 attacks prior to sulfadiazine Third attack lasted over 1 yr.
24	15	NM	12	M.S. M.I. A.S. A.I. C.E.	47		Sulfadiazine
25	10	NF	3	Myo. M.I. M.S. C.E.	3		3 attacks prior to Gantrisin Low WBC Discontinued
26	8	WM	24	M.I. M.S. C.E. Failure	50	? Attack 5/51	4 attacks prior to sulfadiazine Fourth attack, duration 1½ yr.
27	7	WF	12	M.I. C.E.	11		Gantrisin
28	11	NM	6	M.I. M.S. C.E.	20		5 attacks prior to sulfadiazine Sister listed below, No. 29
29	9	NF	1	Failure M.I. A.I. A.S. C.E.	25		4 attacks prior to sulfadiazine Brother listed above, No. 28 Hepatitis, 1953
30	12	WM	1	A.I.	83		3 attacks prior to sulfadiazine
31	8	WF	8	Myo. Failure M.I. M.S. C.E.	78		5 attacks prior to sulfadiazine Sister had R.F.
32	11	WM	8	A.I. A.S. M.S. C.E.	50		Gantrisin
33	12	WM	6	M.I.	38		3 attacks prior to Gantrisin
34	13	WF	15	M.I. M.S. C.E. A.I. Failure	8	Died 9/5/53 Cause not known	5 attacks prior to sulfadiazine Fifth attack, duration 1 yr. Left hospital 6/53
35	5	NF	26	C.E. M.I. Failure	36		Severe failure Acute disease over 2 yr. Sensitive to Gantrisin
36	4	WM	6	No H.D.	72		Sulfadiazine

TABLE III. CONT'D

37	11	WF	54	Myo. A.I. Fibrillation C.E. M.I.	63	Sulfadiazine First attack, duration 3 yr.
38	8	WM	15	M.I. M.S.	35	Gantrisin
39	13	NF	18	No R.H.D. Patent ductus	27	Sulfadiazine Refuses surgery for ductus Pregnancy, 1954
40	8	WM	36	M.I. M.S. C.E. A.I. Failure	69	3 attacks prior to sulfadiazine Third attack, duration 2 yr.
41	10	WF	11	M.I.	44	Gantrisin
42	10	WF	5	No H.D.	12	Sulfadiazine
43	6	NF	28	M.I. C.E. 2-1 Heart block	60	Sulfadiazine First attack at 2½ yr. Second attack at 4 yr.
44	8	NM	11	C.E.	42	Sulfadiazine First attack lasted over 1 yr.
45	10	WF	10	M.I. Myo. Pericarditis	50	3 attacks prior to Gantrisin
46	14	WM	13	M.I. M.S. Myo.	30	3 attacks prior to sulfadiazine (2 with nodules)

TABLE IV. AGE AND DURATION OF THERAPY

	BENZATHINE PENICILLIN G	SULFA
Average age prophylaxis started	10.2	11.0
Average months on therapy	24	38.6
Mean months since onset last rheumatic fever attack	12	9.0

TABLE V. CARDIAC DIAGNOSES

	BENZATHINE PENICILLIN G	SULFA
No heart disease	7	10
Mitral insufficiency alone	10	8
Cardiac enlargement and/or serious valve damage	29	28
Failure	4	8

METHODS

Letters were written to the referring physicians of both groups explaining the project and requesting that additional antibiotics be given only when specifically indicated and that we be notified of their use. The parents of each child also received letters and agreed to cooperate with the project. This eliminated four patients from each group of fifty, and forty-six followed the directions reasonably well.

Eighty per cent of the patients on benzathine and 70 per cent of the patients on sulfonamides were in the hospital or convalescent units of the Medical College of Virginia Hospital during the acute or convalescent stages of their course and therefore carefully followed. It can be clearly seen from Table V that a very large percentage

had heart disease of a serious nature. Seventy-eight per cent of the sulfonamide group had heart disease as did 85 per cent of the benzathine penicillin group.

The benzathine penicillin G group was started in November, 1952, on deep intramuscular injections of 1,200,000 units every twenty-eight days. These patients had initial throat cultures and repeat cultures every three months routinely or at the sign of a respiratory infection. Close contact with the patients and their parents was maintained by an excellent technical assistant so that the attendance rate was remarkably good. Most complained of the injection at first but the slight pain was no serious deterrent and many hardly noticed it. Rare febrile reactions were noted. The patients were seen in rotation, approximately twelve each Wednesday, from November, 1952, through December, 1954. A total of 1,103 injections was given, or an average of twenty-four to each patient in a twenty-six-month study period.

The sulfonamide group was divided with thirty-two on sulfadiazine and fourteen on Gantrisin. These drugs were supplied by the Virginia State Rheumatic Fever Program. They were given according to the schedule previously described, with careful observation of leukocytes and urine in the early weeks. Prophylaxis in these children was often begun prior to November, 1952; hence the longer duration of months on prophylaxis. However, all continued their therapy through the years 1953 and 1954, during the same period as the penicillin group. Throat cultures were also made initially and at three-month intervals, but we were not as successful in getting these more distant patients in for cultures at regular intervals. These patients had a total of 1,776 months on therapy, or an average of 38.6 months.

RESULTS

Benzathine Penicillin G.—Among forty-six patients on benzathine penicillin G there were, in our opinion, no true recurrences of rheumatic fever. During most of the study our laboratory methods failed to distinguish properly the Group A, beta hemolytic streptococci from other groups. We are, therefore, unable to report the influence of the two programs on pharyngeal flora.

One patient, Case 36, had a severe asthmatic bronchitis with aching knees but no heat or swelling, which subsided in two weeks on increased dosage of penicillin. Her sedimentation rate fell to normal in two to three weeks; no cardiac damage was present before, during, or after this episode. Her antistreptolysin titer did not rise.

Two other patients with severe heart disease and failure, Cases 8 and 30, had long-standing carditis which is still smouldering. The first of these is a Negro boy of 13 years who began with rheumatic fever at 6 years of age in 1947. He was seen by us in his second attack in 1951 and was in the hospital for almost a year with subacute bacterial endocarditis, severe rheumatic carditis with mitral valve disease, and cardiac enlargement. In early 1952, he had acute glomerulonephritis and later in the year, evidences of cardiac failure. Failure has become acute several times during the last two years and in November, 1954, he began to fibrillate. Mitral stenosis has become more pronounced and the electrocardiogram has altered from a left to a marked right strain pattern

in the last six months. He has been carefully studied for the possibility of a mitral valvulotomy. He did respond to further digitalis, diureties, and oxygen, and is now ambulatory with a cardiothoracic ratio of 73 per cent. Repeated antistreptolysin titers have been less than 50. We do not believe that he has ever been inactive since 1951.

The patient in Case 30 is a 15-year-old Negro girl whose disease began in June, 1951. She was in the hospital for six months and given cortisone at that time but developed severe cardiac enlargement and mitral valve disease. During 1954, she had been hospitalized four times briefly for pneumonia, fibrillation with failure, dental abscesses, with questionable bacterial endocarditis, and pulmonary edema. Antistreptolysin titers done on each admission were under 50. We consider that her disease also has been constantly active with severe mechanical defects since 1951.

Only one patient (Case 45) had any significant reaction to the drug. She developed an urticarial skin rash with nausea in December, 1953, after one injection. This was thought by a dermatologist to be a penicillin reaction. However, it was not severe and the next month another injection was given with oral Benadryl and no reaction occurred. Subsequent injections have caused no difficulty. This child's mother developed acute rheumatic fever early in 1954.

Sulfonamides.—A clear-cut recurrence has occurred in two patients (Cases 14 and 15) on sulfadiazine. Both of these consisted of severe recurrent polyarthritis with no heart disease present either before or after the recurrence. No positive throat cultures were obtained in Case 14 but in Case 15 a positive culture for beta hemolytic streptococcus was reported a few weeks before the recurrence.

Four questionable recurrences have occurred, but none of these was observed by us. They are discussed below.

Patient 26 had severe heart disease at an early age and was in the hospital for over two years. Six months after discharge he had a sudden fever and chest pain lasting twenty-four hours, responding to morphine and penicillin. His local doctor suggested a flare-up but the story better fits a pneumonic episode, we feel. When seen at the clinic three weeks later, he was at his usual status and no evidence of active rheumatic fever or heart disease could be demonstrated.

Patient 19 had a positive throat culture in February, 1953, and in March, 1953, her local doctor suggested a possible flare-up. She had previous aortic and mitral valve disease and, at the time of the recurrence, had aching joints but no real swelling or tenderness. The sedimentation rate was not elevated; and since she was not seen in our clinic until some months later, it is not possible to be sure about the possibility of a recurrence here.

Patient 16 had headaches and pain in her thighs, but a negative throat culture in March, 1953. This child again had old severe aortic and mitral valve disease but no elevation of sedimentation rate. She did not follow any directions for rest or medications. Her local physician suspected a recurrence, but when seen later in the clinic none was evident.

Patient 34 was a white girl who had severe rheumatic heart disease beginning at the age of 6 years. She was

seen by us at the age of 13 after four previous attacks, and, at the time of admission, was in failure and almost moribund. She remained in the hospital for over a year, receiving cortisone, digitalis, and the best possible care. She was discharged with a cardiothoracic ratio of 69 per cent on June 20, 1953. Until late August, she had done well as an ambulatory patient. A ten-pound weight loss in a two-week period was followed by acute nausea, vomiting, and abdominal pain. Sulfadiazine was discontinued. She was admitted to a small hospital in the western part of the State. It was thought that she had an acute gastroenteritis and so was given intravenous fluids. On September 5, she suddenly died. No further details are known but she was not dyspneic or in obvious failure and had no arthritis. We can only surmise that it was intercurrent infection with severe nausea and vomiting superimposed on an already severely damaged heart.

This leaves a 4.3 per cent recurrence rate, or two patients in forty-six on sulfadiazine. The last four we do not feel justified in including as true recurrences.

DISCUSSION

This series of forty-six cases on intramuscular benzathine penicillin with no recurrence in two years is of some significance when added to those previously reported by Diehl, Stollerman, and Perry.[6, 5, 7] The recurrence rate on sulfonamides of 4.3 per cent is close to the 2.9 per cent on sulfadiazine and 1.5 per cent on Gantrisin reported in Virginia.[3] Other figures of 2 to 4 per cent recurrences on sulfa are available.[8, 9]

This is a marked improvement over the 61 per cent recurrence rate before 1946 in Virginia in an untreated group reported in 1948.[2]

While oral penicillin was not studied in this project, its worth has been soundly established if regular dosage is given.[1]

The advantages and disadvantages of intramuscular benzathine penicillin G given at twenty-eight-day intervals are as follows:

Advantages:

1. Advantages of penicillin, including its bactericidal effect on the beta streptococcus without the emergence of resistant strains so far.
2. Cost of drug less than sulfonamides or oral penicillin.
3. Certainty of dosage.
4. Consistent blood levels.
5. Low rate of reaction.
6. Closer general contact between patient and physician or nurse.
7. Patient and his family kept aware of the constant threat of recurrences.

Disadvantages:

1. Slight transient pain of injection.
2. Monthly visit to doctor's office necessary.
3. Rare reaction to penicillin.

If clinics for intramuscular injection can be established such as have been done with streptomycin for tuberculosis, it is conceivable that many thousands of dollars can be saved for large state programs. Rheumatic fever is a socioeconomic problem and must be so recognized.

SUMMARY

1. One thousand, one hundred three intramuscular injections of 1,200,000 units of benzathine penicillin to forty-six patients with recent rheumatic fever were given for an average of twenty-four months without a single

recurrence. Two patients with old failure and enlarged hearts continue to smoulder but are still living.

2. A similar group of forty-six patients on sulfonamides showed a recurrence rate of 4.3 per cent in an average period of 38.6 months. One child in this group died from what we believe to have been an intercurrent infection and three others had vague aches but no clear-cut recurrences.

3. When added to the previous studies, the evidence is increasingly strong for large-scale use of benzathine penicillin G intramuscularly for prevention of rheumatic recurrences.

We are grateful for the cooperation of the other physicians working with the Virginia State Rheumatic Fever Program; namely, Drs. Louise Galvin, William Spencer, Walter Bundy, Helen Morton, and Pamela Moore. Mrs. Margaret Peple, as technical assistant, has been responsible for the good attendance rate and careful records. Miss Elizabeth Sturt and her nursing staff also assisted greatly.

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PEDIATRIC REHABILITATION AND THE PEDIATRICIAN

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WHILE the traditional role of treatment is to halt, and if possible reverse, a pathological process, the rehabilitation approach is to take the patient beyond that step and to restore him psychologically, socially, and economically to his status before the disability occurred. Such approach requires a group of specialists, including representatives of nonmedical disciplines, working together. This group brings to the problem the utmost in specialization, yet a marked degree of general knowledge. Whether or not the problems of rehabilitation in childhood are of such specialized nature as to justify the concept of "pediatric rehabilitation" is still open to question. Obviously, the pediatrician will be called upon to treat intercurrent infections, diagnose skin rashes, and to administer prophylactic inoculations. To what extent he can play a positive and directive part in this field is now being debated, and the answer will depend on how much interest, energy, and study he brings to the problem.

In this paper we describe a rehabilitation unit for children in which the place of the pediatrician is conceded to be important. The principles of rehabilitation as applied to childhood are enumerated and the organization and administration of a rehabilitation team are described. We hope the need in a pediatric department for a division of pediatric rehabilitation will become evident.

Rehabilitation refers to that discipline in medicine which is concerned with the restoration of an incapacitated individual to the milieu which he occupied before the incapacity developed. The concept is complicated in children. In dealing with congenital or neonatal illness there is often no previous normal status, no physical, psychological, and social milieu to return to. It becomes a question not of teaching a man to walk again who once walked, or a patient to talk again who once talked. We have to teach skills the child has never possessed, and to stimulate the development of functions for the first time, so that in childhood we often speak of habilitation rather than rehabilitation.[1]

We wish to enumerate five principles applicable to rehabilitation in general, but especially pertinent to pediatric rehabilitation. The first can be exemplified in a short phrase which is virtually the motto of our department at the Jewish Chronic Disease Hospital: "let's try." In previous decades many of the children handled here were considered medical curiosities, and seemed fit only for the back pages of pediatric journals. The present policy is to re-evaluate every child brought to us from the point of view of curability.[2-5]

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The second principle is to think in terms not of what the child lacks, but rather in terms of what remains. A child who has flaccid paralysis of both lower extremities following poliomyelitis still has a mind and normal upper extremities. A child with spastic paralysis of the lower extremities retains many normal muscles, and even the abnormal ones may possess a measure of innervation. Careful evaluation may determine how best to use what remains.

Ambulation with crutches is neither graceful nor efficient, but it can be effective, and with a normal mind, the child can be taught to accept this method of locomotion and rise above it to a full, rewarding life.

The third principle is to treat dysfunction rather than sickness. For example, the treatment of flaccid paralysis is quite the same whether due to poliomyelitis or spina bifida. Urinary incontinence is treated on the basis of what cystoscopy, the cystogram, and pressure studies show us about the action of the detrusor muscle, whether the abnormality of this muscle is caused by spina bifida, transection of the spine, or transverse myelitis.

Fourth, on the rehabilitation ward treatment is directed not only to a disability, but to the total child. We not only dry him up, or ambulate him; we educate him, assess his economic potentialities, stabilize his mind in relation to the difficulties of his situation, and go into the home to reorient his environment in a manner necessitated by the circumstances. In children we deal not with a static disability; we have also the process of physical and mental growth which should go on despite the handicap. An adult with an amputated leg needs only restoration to health and his job. The child with a congenital amputation, who has lived all his life in a hospital, must receive an education, must be made aware of the physical nature of the world about him, and we have even found it necessary to awaken in him such concepts as home, mother, father, and God. Moreover, in an actively growing organism provision must be made not only for harmonious development, but against the greater possibility of secondary disabilities arising in a growing organism with a disturbance in growth pattern. Finally, in this field, since one deals with a pathologic process after the question of survival has been decided, one tends not to make decisions urgently, but rather to evaluate calmly and slowly all disabilities from the point of view of long-range restoration.

Since many physicians must participate in the care of a handicapped child, there has developed the concept of a team, a concept which is the outstanding contribution of this specialty to modern medical practice. Ours consists of a primary group of medical specialists, including pediatrician, orthopedist, urologist, neurologist, psychiatrist, logopedist, and physiatrist. In addition, there is an essential ancillary group of nonmedical specialists, including psychologist, speech therapist, vocational consultant, physical and occupational therapists, schoolteachers, nurses, and social workers. This team is usually presided over by a coordinator. We have not separated the professional group from the ancillary as has been suggested;[6] constant interaction of medical and nonmedical specialists,

working together at the same conference, seems to us, as it has to others,[7] mutually beneficial.

Members of the team act both individually and as a unit. When admitted, a patient is subjected not only to the usual pediatric "work-up," but also a host of diagnostic and evaluation procedures. The medical diagnosis per se is often part of his admission note: poliomyelitis, "cerebral palsy," spina bifida, arthrogryposis, blindness, deafness, speech abnormalities, hydrocephalus, Erb's palsy, Riley-Day syndrome, epilepsy, torticollis, amyotonia congenita, muscular dystrophy, myasthenia gravis, chondrostrophy, hip dislocation, arthritis, trauma of the musculoskeletal or nervous systems, the various ankle deformities, scoliosis, joint injuries, bronchiectasis, or heart disease. During the first two to three weeks, members of the team act as individuals, and their chief concern is to measure both the disabilities and functional residues in terms of their own specialties. Usually the patient is presented at the various intradepartmental conferences. At the end of this preliminary period, the child is ready for his first evaluation conference.

The evaluation conference is presided over by the coordinator. A pediatrician who has had training or experience in rehabilitation can best fulfill this function for the child. The coordinator introduces the patient and states the nature of the problem. Disabilities generally belong to one of three groups: (1) musculoskeletal disability, (2) communication disability, (3) visceral disability, such as bladder incontinence or cardiovascular weakness resulting from disease or from prolonged skeletal distortions. Of the musculoskeletal disabilities, interference with walking is the most restrictive. Failure may be due to flaccid paralysis or spasticity of the musculature of the spine and lower extremities, or to their abnormal movement. It may also result from contractures, often due to neglect. Involvement of the upper extremities may interfere with ambulation if the arms are needed to wield a pair of crutches. Disability of the upper extremities more specifically affects the movements and maneuvers needed for self-care in the bedroom, bathroom, and dining room, as well as the manipulations with which to earn a livelihood.

Communication disability may be due to deafness or to speech imperfection. The latter may result from anatomic malformation, as in cleft palate, or to paralysis or abnormal movement of the required musculature. In the larger number of cases, however, inability to communicate results from inadequacy of the cerebral centers.

Urogenital disabilities may be primary, such as ballooning of the ureters due to interference with innervation, or, secondary, such as ballooning of the ureters secondary to obstruction of the posterior urethra. Stone formation may be secondary to sudden arrest of weight-bearing and consequent decalcification of the bones, or it may follow repeated infections in a paralytic bladder. Children with rheumatic or congenital heart disease receive the usual medical treatment, but also are treated by the rehabilitation approach, including orientation, play and occupational therapy, psychologic and psychiatric evaluation,

vocational and educational guidance, and detailed attention to home environment.

The coordinator, after his statement of disabilities and resources, and usually after an analysis of the basic problems in order of urgency, will then ask the psychologist to give his findings. Rehabilitation is largely a matter of teaching what is left to take over the function of what is gone. Teachability is the largest factor in success or failure. If the child has had polio, we hope to teach him to use the muscles which have survived rather than attempt to restore function to noninnervated muscles. If the child has spina bifida with flaccid paralysis of the lower extremities, he may have to learn to walk by using the shoulder girdle to manipulate crutches. Speech therapy is valueless if the child cannot organize thoughts, and there is no point in teaching lip reading if the child cannot understand ideas. This factor of teachability makes the child the most important member of the rehabilitation team.

The psychologic evaluation is reported and interpreted with great care, for it determines whether or not we can undertake a full rehabilitation program. Testing is not a routine matter, and often repeated batteries of tests are required before a proper evaluation is arrived at. Members of the team learn not to be misled by prejudice, not to ascribe low levels to patients because of facial distortions, abnormal movements, speech difficulties, unusual postures or inability to perform because of muscular rather than mental deficiency. The schoolteacher and the social service worker may be able to add important data in this area.

The physiatrist gives a complete report on the musculoskeletal system. This may include quantitative testing of muscle function clinically or by electrical stimulation, an estimate of primary and secondary joint involvement, and an estimate of teachability. He will usually report on the types of exercises which may serve either to maintain the function of healthy muscles or to restore function of the diseased muscle where possible, to maintain mobility of joints, and to prevent the metabolic disturbances following immobilization. The physiatrist and the members of his department are the cornerstone of the team. His occupational therapist will engage the patient in activities for diversion or for the exercise of fine manipulative movements. In this department, also, is begun that training in numerous skills which are essential requirements for the activities of daily living, and which also lay the groundwork for a vocation.[8] The patient may have participated already in group activities: the rhythm band, wheelchair square dancing, or moving pictures designed for orientation into the world outside the hospital walls. The functions of the speech therapists on our team have been adequately described;[9] they are members of the physiatrist's staff.

It is important to emphasize that the physiatrist is not only a specialist in physical medicine but an expert in rehabilitation. As a member of the team whose specialized training cuts across most of the other specialties, his judgment is frequently decisive. To him often falls the decision of

brace versus arthrodesis, of ureteral transplant versus indwelling catheter, early or late ambulation, and the difficult question of bedsores.

The orthopedist usually discusses the possibility of surgical intervention. Operations are generally of two types, either to loosen up a stiff joint or to stiffen a loose one. In the former category are the capsulotomies, neurectomies, tendon-lengthening procedures, and muscle transplantation. They are performed chiefly in spastic paraplegia and in neglected paralysis of various types in which contractures have developed. Fixation of a joint is usually performed to maintain functional position, as by arthrodesis of the ankle bones, arthrodesis of the shoulder to permit movement of an arm by action of the trapezius muscle on the scapula, or arthrodesis of the thumb to facilitate thumb-finger approach. Where paralysis prevents the finer movements of the fingers, tendon transplant with or without joint fixation may help.

The urologist reports on the status of the bladder and the influence of the disease on kidney function. He may advise a permanent indwelling catheter, or suggest one of the various devices to catch urine and maintain a reasonable dryness of the perineum. On the other hand, he may suggest ureteral transplantation into healthy skin or into a loop of gut which then empties into a cecostomy bag. For an atonic bladder he may advise excision of the vesical neck. Ofttimes he may find no physical reason for incontinence and advise intensive treatment by the psychologist.

The psychiatrist will report on functional disturbances associated with or resulting from the illness, and may also report on the psychiatric disturbances in the family.[10] This theme may be elaborated upon by the social worker who will also present detailed data relating to home and family.[11] The logopedist will present the results of his studies of hearing and speech. The schoolteacher will report on his general behavior and adaptability, as will the ward nurse. The vocational consultant may make general observations or he may defer action until the rehabilitation program has been under way.

Two additional members of the rehabilitation team may now be introduced. The first is the patient himself. Some patients respond well to rehabilitation and some do not. The factors which determine this phenomenon are being studied by the psychologists on our team. Whatever the reasons, the patient is an important member of the team, and the results depend on his willingness or ability to participate. Cultivation by the pediatrician of this team member may often spell the difference between success and failure. Too often such cultivation is neglected, and the resulting failure is covered up by labeling the patient as unintelligent, malingering, lacking in motivation, or neurotic.

The other member of the team who should be mentioned at this point is the parent. The contribution of the parent in rehabilitation depends greatly on the efforts of the pediatricians, and we will describe the relationship later.

The function of the pediatrician on the rehabilitation team interests us most at this time. His functions may be discussed under four headings: as

pediatrician, as coordinator, as surrogate, and as investigator. In our hospital the pediatrician carries both diagnostic and therapeutic responsibilities. The popularization of such terms as "cerebral palsy" has tended to obscure the need for exact neurological diagnosis and localization. While the specialist on the team will tend to state the problem in terms of a complex of disabilities, the pediatrician is better fitted, particularly with the very young patient, to unify the diagnosis and identify the complex of findings with some established syndrome. Other duties related to diagnosis arise during hospitalization. The pediatrician obtains a history which will present an integrated story of the child's physical, psychologic and sociologic problems. He delves into the individual and family story for a possible etiology. He studies the factors, from Rh incompatibility to dietary imbalance, which may affect the incidence of inborn defects. He keeps together as a single story the developing chart record bulging with the opinions of the medical and ancillary specialists.

From a therapeutic point of view the child's interest is best served if the pediatrician does not limit himself to the management of the patient's nutrition, immunization, and occasional illness. His role in actual treatment will depend on his experience in this field. Especially important is his position as arbiter. In the total rehabilitation of a child there are indications and contraindications above and beyond those in the armamentarium of the individual specialist. A special sense for these can be developed by the pediatrician with e x p e r i e n c e in rehabilitation. His weight may be decisive as regards one or another procedure if there is divergence of thought. Sometimes he will reject on physiologic grounds a line of treatment suggested by either the orthopedist or the psysiatrist. Occasionally he will have to arrest a certain enthusiasm for technical procedures which do not encompass the patient's needs. Ofttimes he will reject pessimism which deteriorates into lethargic inactivity, and will insist upon reconsideration of the patient's needs, and fresh exploration of methods to meet them.

In his function as a coordinator, the pediatrician has as one of his more onerous duties to decide whether or not a child should be admitted for evaluation. If the decision is affirmative the coordinator initiates and supervises the period of individual consultations by specialists, and later arranges for the first evaluation conference. At this conference he acts as chairman and in this capacity his most difficult task is fitting the various disciplines into a harmonious therapeutic entity. For example, the orthopedist may urge an operation to remedy the scoliosis in postpolio. However, if this means placing the child in a cast for six months and running the risk of kidney damage from decalcification, or if it may precipitate psychiatric upset, it must be deferred. The urologist may guarantee a dry perineum after a ureteral implantation, but this may have to be deferred for the sake of a triple arthrodesis which will enable the child to walk better. Or the coordinator may ask approval for a test period to observe the effect of stretching, followed by a brace on a tight Achilles tendon, before acquiescing to

tenotomy. Decisions by the team are rarely made by vote. The coordinator discourages desultory observations, curtails interdepartmental wrangling, and promotes discussion until general spontaneous agreement is reached. He then dictates a summary of findings and lays down the sequence of the proposed rehabilitation procedures.

In the succeeding weeks the pediatrician-coordinator will, in effect, maintain a continuous evaluation process. He studies and records the results of exercise, of occupational therapy, of conservative orthopedic manipulation, and of all other aspects of the treatment in order to report back to the evaluation conference the data on which the team will make its next decision. He schedules operative procedures and prepares the patient and his parents for them. If physical therapy is needed after an orthopedic operation, and this is so in most instances, the pediatrician sees that the physiatrist is alerted. The wishes of the physiatrist are conveyed to the orthopedist, those of the play therapist to the social worker; the observations of the schoolteacher are brought to the psychologist, and the observations of the ward nurse are relayed to the urologist.

The pediatrician's role as coordinator is most useful in the realm of psychologic disturbances. All physically handicapped children suffer psychologically, but few require the aid of a psychiatrist. Most of their difficulties can be handled by the psychologist in consultation with the pediatrician. The practical implications of such problems, as they influence the rehabilitation process, are best brought to the attention of the team by the pediatrician. Moreover, psychometric evaluation often needs interpretation to the team, and this is best performed by the pediatrician.

In his capacity as surrogate the pediatrician exercises a most complex responsibility. Many of the decisions which the physician is called upon to make for or with the handicapped child deal with matters which are not medical but parental and domestic. Shall the child go to school, and to what kind? Shall he play with the other children on the block? Will he perpetuate his defect? Should he receive religious instruction? Shall he remain at home or be institutionalized? Some of these questions bewilder the parents of normal children. In the handicapped child, the parents almost inevitably delegate their rights to the doctor, who should be a pediatrician.

The pediatrician is confronted by the psychologic and social effect of the child's illness on the parent, the sense of physical and social inadequacy, the feeling of guilt, the indecisiveness regarding additional children, the self-pity, the financial strain, the awful uncertainty of the future. The highly charged psychologic atmosphere enveloping the chronically ill child and his family, and the accentuation of the tensions by the intrusion of the physician into the affairs of the family, essential but the more offensive because it is unavoidable, has already been described.[10] To deal with these problems the pediatrician needs not only the best training, experience, and attitudes of his specialty, but the close cooperation and helpfulness of all members

of the team, especially the social worker, the psychologist, the nurse, and the schoolteacher.

The pediatrician can play an important role as investigator. At the evaluation conference, many disciplines vie for therapeutic priority. We already possess much controlled experience in the individual specialties for isolated procedures skilfully perfected for the attainment of circumscribed goals. We now need controlled observations and clinical experimentation to determine the best sequence for the various therapeutic undertakings. Clearly defined indications are required to delimit the extent to which one therapeutic objective should be met before a second is undertaken and, on the other hand, what procedures can be safely carried out simultaneously. What, for example, is the proper treatment for equinovarus in a 6-year-old boy with cerebral palsy? The orthopedist may suggest lengthening the Achilles tendon. The question arises as to a concomitant abductor neurectomy. However, the operation may result in too loose an Achilles tendon. Moreover, even if successful, the child will have to wear a brace to prevent relapse, so that the question arises as to stretching the foot into normal position, and keeping it there with a brace since such a device may actually lengthen the tendon; if it does not, the child can walk reasonably well with a permanent light brace. Another example of needed studies in integrated rehabilitation is an investigation of the psychologic, urologic, surgical, orthopedic, and nursing problems involved in the maintenance of perineal cleanliness and dryness in patients with spina bifida, and the prevention of trophic ulceration. Also needed is study of the effects of handicaps and the rehabilitation procedures on growth and metabolism. Study of bone decalcification and elaboration of practical methods to determine it quantitatively are important.

The psychologic problems in rehabilitation need much elucidation. A preliminary investigation of the methods for successful utilization of parental helpfulness has been reported.[12, 13] In the treatment of the child himself we have noticed there is a period of lag between beginning of treatment and the time the patient commences to participate actively and cooperatively in the various manipulations. During this refractory period the child is apprehensive, suspicious, tearful, or lackadaisical. Sometimes the refractory period ends when the "right" physical therapist appears, but usually the factors causing it or influencing its termination are obscure. A cooperative study by pediatrician and psychologist of the child's behavior in the gymnasium, tank, and therapy rooms may furnish a clue to this phenomenon.

The problem of how to predict the patient's response to rehabilitation is of great practical importance. Intelligence is not the only factor, but there are also considerations lumped under such terms as "motivation" and "acceptance" which need elucidation. While some studies along these lines have been made for adults[14] no similar studies have considered children. Moreover, the methods of psychologic evaluation and their clinical application need continued study, and it is difficult to see how this type of investigation can be carried out with-

out the active participation of the pediatrician. Finally, an important problem for investigation is that of the coordinator function itself. Especially needed is much more study in the methods of doctor-patient, doctor-doctor, doctor-technician, and doctor-parent coordination.

SUMMARY

1. The field of pediatric rehabilitation is new and stimulating, and is worthy of our best efforts.

2. The number of diseases best treated by the rehabilitation approach has increased.

3. The four basic principles of pediatric rehabilitation can be characterized by the following phrases: (a) let's try; (b) what's left? (c) function, not disease, determines treatment; (d) rehabilitation involves total care of the child; and (e) rehabilitation is a long-term undertaking.

4. The most important areas for rehabilitation are: (a) musculoskeletal disability; (b) communication disability; (c) visceral disability.

5. The rehabilitation teamworking through an evaluation conference is the most important part of the armamentarium in pediatric rehabilitation.

6. Teachability is the significant limiting factor in rehabilitation. The patient is, therefore, the most important member of the rehabilitation team.

7. The pediatrician on the team functions as pediatrician, coordinator, surrogate, and investigator.

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ACCIDENTAL INGESTION OF POISONS

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THE accidental ingestion of toxic materials by children is preventable. Where then may we best attack this problem of poisoning? In an effort to answer this question, a statistical survey was made of children seen at Children's Memorial Hospital, Omaha, with a history of ingestion of poisonous or potentially poisonous materials. This survey extended from March 15, 1948, to Jan. 1, 1954, and included patients seen in the outpatient department and those admitted to the hospital.

There was a total of 472 outpatients. The number of outpatients increased from thirty-six patients in 1949 to 154 patients in 1953. This increase did not indicate an actual increase in the percentage of poisonings, but rather paralleled a general increase in the total number of outpatients seen.

There was a total of 104 patients hospitalized. The hospital admissions ranged from five patients in 1949 to thirty-eight patients in 1953. It would not be significant to represent this as a percentage of total hospitalized patients as the criteria for hospitalization is variable. Hospitalization depends not only on the clinical picture and type of poison ingested but also on the human variations in cautiousness on the part of the physician.

The poisonous materials were divided into five groups: (1) medicines; (2) hydrocarbons; (3) household cleaning agents; (4) insect and rat poisons; and (5) miscellaneous.

There were sixty-seven drugs in the group of medicines. Ten different hydrocarbons and fourteen agents for household cleaning were ingested. There were ten different insect and rat poisons. The miscellaneous group included thirty-seven products too variable to classify. The distribution of these five main groups among the outpatients is shown in Fig. 1 and among hospitalized patients in Fig. 2.

The six most common medicines ingested by those treated as outpatients were aspirin, laxatives, thyroid, sulfonamides, cough syrup, and boric acid. Aspirin was encountered in one-third of the outpatients ingesting medicine. The aspirin, laxatives, thyroid, and sulfonamides were in tablet and pill form. Many of the cough syrups contained codeine. The boric acid was ingested either in the crystal form or as solutions mistakenly drunk for water.

Patients were most commonly hospitalized for ingestion of aspirin, barbiturates, and camphor (campho-

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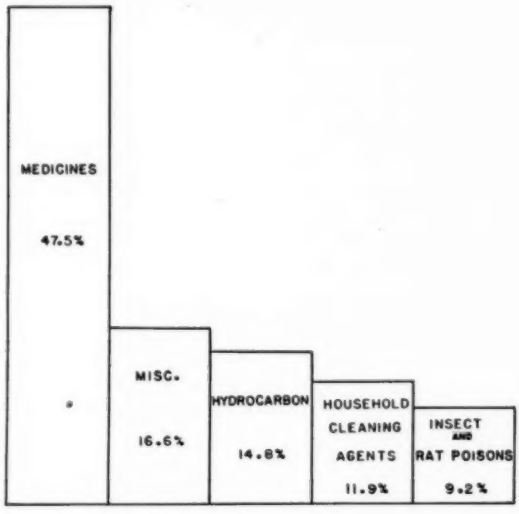
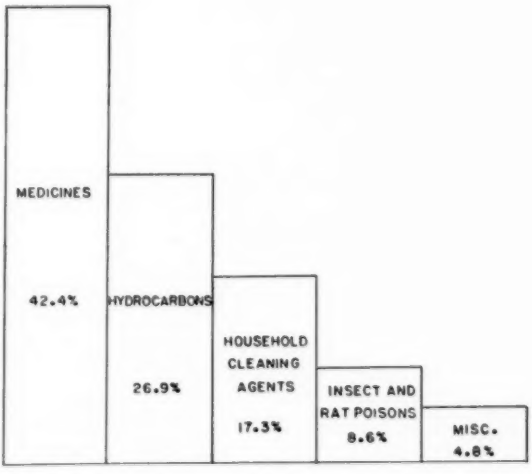


POISONING — OUT PATIENTS

Fig. 1.



POISONING — HOSPITAL ADMISSIONS

Fig. 2.

ated oil). Aspirin was again the most commonly encountered, making up 29 per cent of those ingesting medicine. Admissions for aspirin poisoning were most common because of sheer numerical predominance of aspirin ingestion. Children ingesting barbiturates were hospitalized frequently due to the potential hazard of deep sedation and occasionally for extreme restlessness. One-half of the hospitalized patients ingesting camphorated oil had generalized convulsions.

The percentage according to sex showed the incidence of ingestion in both boys and girls to peak during the 1- to 3-year age period. The incidence of poisoning in boys was higher than girls in this age group. After 3 years of age there was no significant age difference. This was similar in both outpatients (Fig. 4) and hospital patients (Fig. 5).

Ingestion according to sex showed that 59.9 per cent of the outpatients and 61.5 per cent of the hospital patients were boys. Girls represented 40.1 per cent of the outpatients and 38.5 per cent of the hospital admissions. This emphasizes a known basic sex difference in the investigative nature of the male child, especially in the 1- to 3-year age group.

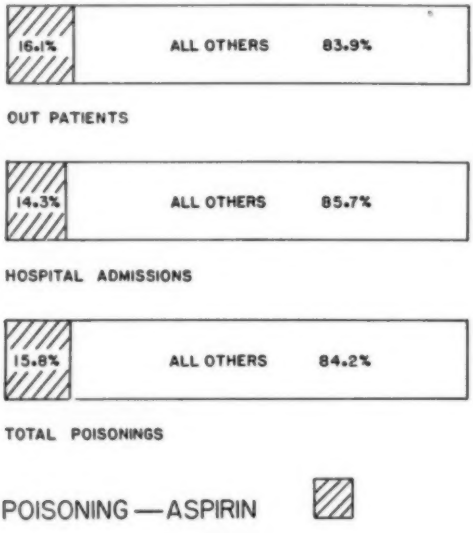
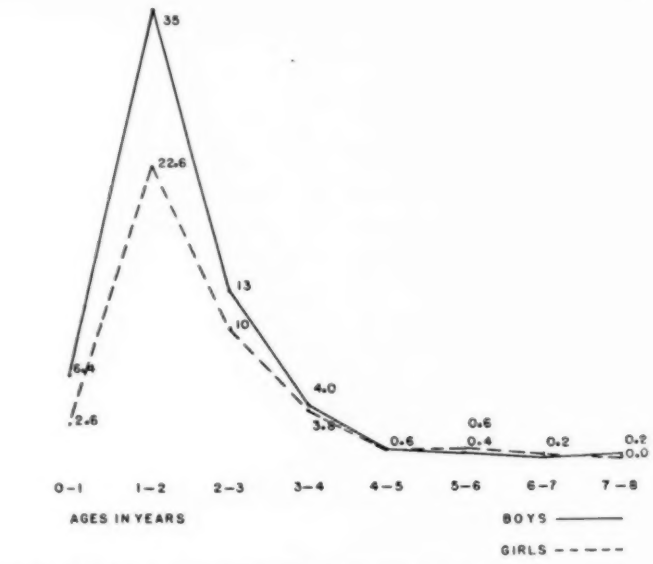


Fig. 3.

The percentage of the poisoning problems from aspirin alone is shown in Fig. 3 in relation to outpatients, hospitalized patients, and total poisoning problems.

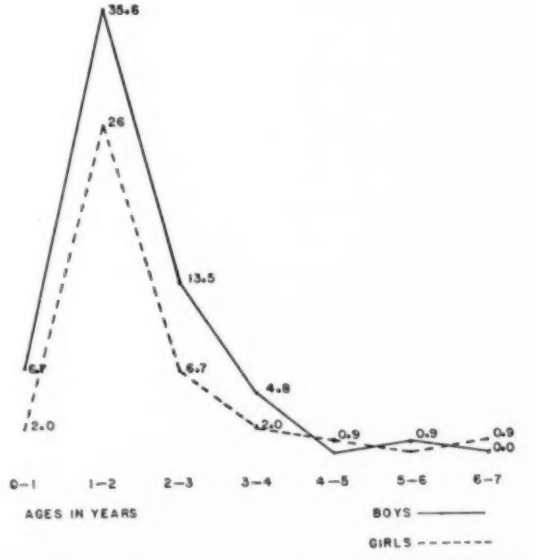
The majority of the children seen were in the age group between 1 and 3 years of age. This age group alone made up 80.6 per cent of the outpatients and 81.8 per cent of the patients hospitalized.

There were five deaths. The deaths were due to the ingestion of Nupercaine ointment by a 2½-year-old female; turpentine by a 1½-year-old



POISONING — PERCENTAGE ACCORDING TO SEX (OUT PATIENTS)

Fig. 4.



POISONING — PERCENTAGE ACCORDING TO SEX (HOSPITAL ADMISSIONS)

Fig. 5.

male; iron pills by a 1½-year-old female; Pride furniture polish by a 1-year-old male, and Dibistine antihistamine tablets by a 3-year-old female.

SUMMARY AND CONCLUSIONS

Medicines constitute the largest group of poisoning problems. The elimination of this group alone, which is probably the most easily preventable, would reduce poisonings by about 45 per cent. The elimination of aspirin alone would reduce the total poisonings by 15 per cent. It should also be emphasized that households with children between the ages of 1 and 3 years of age should be especially vigilant, particularly if these adventurous youngsters are boys.

Accidental Poisoning in Children Is Not New

We hear from Penns-neck (in West-New-Jersey) that a few days ago, Mr. John Redstrake's Son of about 3 Years old, his Servant Boy, & Negro Woman, having eaten some Mushrooms, were all three taken with Swelling soon after they had eaten them, and kept swelling till they died, which was not long after.

AMERICAN WEEKLY MERCURY, July 24, 1735.

We hear from Jamaica, Long-Island, that a little Child of Mr. Betts, being at play in the grass by the door, picked up a small Toad, and played with it, the mother discovered the Child having it in its mouth, but too late, although all methods were taken, yet the Child began to swell and died on the fifth day.

CONNECTICUT JOURNAL (New Haven), June 19, 1793.

ERYTHRODERMA DESQUAMATIVA OF THE NEWBORN INFANT

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A FAMILIAL aspect to erythroderma desquamativa has been emphasized in a recent report.[1] In view of the fact that such observations may shed new light on the pathogenesis of this obscure disease, a similar instance is reported.

Leiner's disease[2] is described as a generalized exfoliative dermatitis appearing most likely in the newborn infant who is breast fed, but may also occur in older and artificially fed infants. The desquamation may vary from fine scales to large flakes and may be dry or the greasy seborrheic type. The entire integument may be involved and in some cases there is shedding of the fingernails and toenails. Although many of these infants' skins return to normal, most of the severe cases with early hypoproteinemia associated with toxemia and edema usually tend to a fatal termination.

Erythroderma desquamativa of the newborn infant was first described in 1907 by Carl Leiner. Glaser and Markson[3] reviewed the subject in 1945 and called attention to the low serum protein, liver damage, and pancreatic changes found in these infants. These authors stated that the serum protein level is indicative of the prognosis. Since 1945 very few articles have appeared in the American literature concerning this disease. Thelander[4] reported that her patient, after recovering from erythroderma desquamativa, developed celiac syndrome. The presence of duodenal ulcers and an increase in the antidiuretic hormone in the cerebrospinal fluid of infants with erythroderma desquamativa has recently been observed.[5] In 1954 Charles Brant reported two cases occurring in the same family and suggested a familial aspect to this disease.

The disease has been thought to be due to toxic responses to pathogens generated in the gastrointestinal tract,[6] hormonal disturbances,[7] congenital defect in the skin,[8] allergic reaction imposed upon seborrheic dermatitis,[9] or caused by the use of ill-advised local medication on a simple dermatitis.[10]

The case to be presented is remarkable in that the infant was the third case to occur in a single family. The disease which caused death in all three infants manifested itself on the first day of life and only the male infants were affected.

CASE REPORT

M. P., a white male child, born May 15, 1951, was admitted to the Gaston Memorial Hospital newborn nursery immediately after birth. He was the seventh offspring of a mother aged 27 years and a father aged 47 years. This is the father's second marriage. There were no children by

Address: The Children's Clinic.

his first wife. Family history revealed that the paternal grandfather had asthma. The six previous pregnancies terminated as follows:

In 1940 the first-born infant was a male who developed erythema and desquamation of the skin the first day of life. This condition was present during the eleven days that the infant lived.

In 1941 a normal female infant was born who is living and well.

In 1943 the second male infant was born. He was jaundiced the day of birth and within a few hours erythema and desquamation began. This continued throughout the four days of life.

In 1945 a normal female infant was born who is living and well.

In 1948 the third male infant was born and he is living and well.

In 1950 the fourth male infant was born and was normal in appearance and is living and well.

During her seventh pregnancy the mother had good prenatal care. Her serologic test for syphilis was negative and her blood type was A Rh positive. She received calcium and iron tablets. This pregnancy was complicated by bleeding from the vagina during the second month and by the onset of herpes zoster during the last month of gestation. She received no x-ray therapy for the herpes zoster. Ether anesthesia was given at the time of delivery. The labor and delivery were described as normal. The infant's birth weight was 6 pounds 3 ounces. The mother saw the infant one hour after delivery and stated that this baby had the same disease that killed two of her other children.

When the infant was examined on the day of birth the skin was red and desquamation had begun on the back of the hands. The next day the skin of the entire body had become dry, and when an area of the outer layer was removed a red, shiny, moist underlying layer was present. By the third day of life the scalp was crusty, with yellow seborrheic-like rash, and some of the hair was falling out. The outer layer of the scalp, including the hair, was easily removed when the scalp was cleaned. The eyelids became leathery and the eyelashes were scant. The eyebrows disappeared by the third day of life and there was a foul odor to the now icteric skin. The nostrils were filled with desquamated skin and a purulent discharge developed. Monilia infection of the lining of the mouth and the tongue was present. The tongue showed no evidence of desquamation. No other abnormalities were noted at this time.

The infant was not allowed to nurse the breast but was given an evaporated milk and Karo syrup formula the second day of life. He took the formula poorly and by the third day of life had lost 1 pound 8 ounces. Penicillin and streptomycin were begun intramuscularly as was ACTH, 5 mg. every six hours. Subcutaneous fluids consisting of glucose and saline solutions were given. The skin was cleaned with mineral oil. Olac formula was substituted for the evaporated milk formula. The ACTH was continued, and by the tenth day desquamation of the skin was nearly complete. The general condition of the baby had improved and he began to gain some weight, gaining to 5 pounds 11 ounces by the seventeenth day. The odor to the skin had disappeared, and ACTH was discontinued. The Olac formula was replaced by Mulsoy. After this time it was extremely difficult to maintain his weight which remained throughout the rest of his life between 4 pounds 12 ounces and 5 pounds 11 ounces. There was also extreme difficulty in maintaining normal body temperature. Despite the use of an incubator, the rectal temperature was often as low as 94° F. and as high as 104° F. Frequent edema of the hands and lower extremities occurred and continuous oozing resulted from the desquamated areas. By one month of age the skin appeared as shown in Fig. 1.

At this time ACTH and Olac formula were again tried but no improvement in the skin was noted. Mineral oil was used during the first few weeks to clean the skin, then petrolatum was used. Ointments containing penicillin, Furacin, crude coal tar, Myciguent, as well as 2 per cent salicylic acid in petrolatum were used on the skin without improvement. For periods of several weeks no local treatment of any type was used.

When the infant was 4 months old, cortisone was given by mouth. At first 12.5 mg. was given every six hours and this was later increased to 25 mg. every six hours. Potassium citrate was given during this time. No improvement was noted and no cortisone or ACTH was given during the last month of life. Blood transfusions were given when the red blood count fell much below 3,000,000 per cubic millimeter. Human albumin was given intravenously on two occasions, but the infant became cyanotic and his condition became critical, with evidence of pulmonary edema developing after each injection. This occurred after only 4 or 5 c.c. had been given slowly. The infant developed pneumonia and atelectasis when 5 months of age and died a few days later.

Laboratory data were as follows: On the day after birth the hemoglobin was 14 grams; red blood count was 5,500,000; white blood count was 19,300 of which 72 per cent were polymorphonuclear leukocytes, 22 per cent were small lymphocytes, 1 per cent was large monocytes, 2 per cent were basophils, and 3 per cent were myelocytes. The blood type was A Rh negative. On the second day of life the carbon dioxide combining power was 20 meq., chloride was 78 meq. per liter, and total protein 3.5 grams. During the first month of life the eosinophil count ranged from 400 per cubic centimeter to zero, depending on the amount of ACTH being received by the infant.

Fig. 1.—Infant one month of age, showing scaly desquamation of the outer layer of the skin with a red, moist, underlying layer present.

At 1 month of age the hemoglobin was 11.8 grams; red blood count was 4,350,000; white blood count was 22,600 with 12 per cent small lymphocytes, 7 per cent large lymphocytes, 5 per cent monocytes, 75 per cent polymorphonuclear leukocytes, and 1 per cent eosinophils.

By 2 months of age the red count had dropped to 2,720,000, and at 3 months of age the red blood count was 3,300,000. By the fourth month, despite transfusions of whole blood, the hemoglobin was found to be 5.8 grams and the red blood count, 2,550,000.

The day before death the total protein was 5.05 grams, with albumin 3.14 grams, globulin, 1.91 grams, and A/G 1.6.

X-ray examination of the chest first showed densities suggesting pneumonitis in the right mid-lung field at 2 months of age. At 4 months of age the chest films showed marked pulmonary emphysema with marked accentuation of the bronchial markings in both lung fields. Shortly before death there was x-ray evidence of pneumonia and atelectasis in the right middle lobe and bilateral pulmonary emphysema.

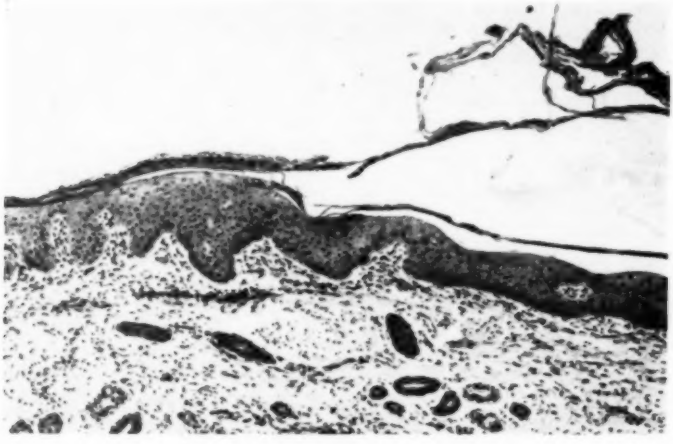

Fig. 2.—Low-power photomicrograph showing exfoliation of layer of parakeratotic epithelium and mild inflammatory infiltrate in superficial corium.

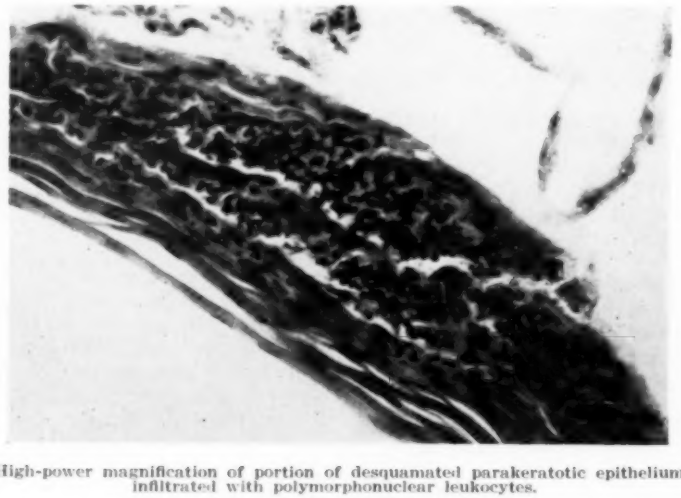

Fig. 3.—High-power magnification of portion of desquamated parakeratotic epithelium heavily infiltrated with polymorphonuclear leukocytes.

Post-Mortem Examination.—This was done by Dr. Paul Kimmelstiel, Department of Pathology, Charlotte Memorial Hospital. Careful gross

and microscopic examination of all organs revealed pathologic findings only in the skin and in the right lung, the latter showing rather massive atelectasis and minute foci of bronchopneumonia alternating with areas of emphysema. Specifically there were no abnormalities in the liver, pancreas, and duodenum.

Numerous sections through the skin from various portions of the body revealed essentially the same pattern of pathologic changes (Fig. 2). Within a rather narrow subepidermal zone the corium is rather hyperemic, and between the prominent capillaries is found a relatively loose infiltrate of small round cells mainly composed of lymphocytes and histiocytes but free from polymorphonuclear leukocytes. The epidermis shows extreme parakeratosis. A granular layer is difficult to identify in most sections. Large portions of the parakeratotic layer are desquamated, being loosely attached at few points to the underlying coherent portions of epidermis, thus forming structures reminiscent of empty intraepidermal, superficial bullae. In many areas the desquamated parakeratotic layers are heavily infiltrated with polymorphonuclear leukocytes.

DISCUSSION

A case of a male newborn infant with erythroderma desquamativa is presented. Two male siblings had also died of the disease; however, the other four siblings, both male and female, have remained clear of any abnormality.

The exfoliative dermatitis was present on the day of birth and lasted throughout the infant's life, resistant to various types of local treatment and change of formula. Some improvement of the skin and general condition of the infant was noted when ACTH was first administered, but this was only temporary. Cortisone did not seem to influence the course of the illness.

It was difficult to maintain the infant's normal body temperature. Antibiotic therapy did little to check the secondary infection. A gradually progressive anemia developed, and after an initial weight gain during the third week of life normal nutritional balance could not be maintained. This, combined with the continuous weeping of the skin, was probably responsible for the hypoproteinemia, particularly in view of the absence of pathologic findings in the liver parenchyma at the time of death.

It is conceivable that erythroderma desquamativa of the newborn infant could be confused clinically with Ritter's disease. However, the general appearance of the infants is different in the two diseases. In erythroderma desquamativa the desquamation of the skin consists of scales and flakes with greasy seborrheic dermatitis of the scalp, while in Ritter's[11] disease the desquamation of the skin usually occurs in sheets, leaving large, denuded, reddened, dry areas.

It seems likely that a significant difference may exist between erythroderma desquamativa present at birth or developing during the first few days of life and erythroderma desquamativa superimposed upon "infantile eczema" as a precursory condition. "Primary" erythroderma desquamativa may occur in siblings and seems to have a more grave prognosis than "secondary" erythroderma desquamativa.

SUMMARY

A case of a male newborn infant with erythroderma desquamativa is presented. Two male siblings had also died of the disease.

It is suggested that there are significant differences between "primary" erythroderma desquamativa of the newborn infant and "secondary" erythroderma desquamativa where infantile eczema often exists as a precursor.

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CALCIFICATION OF THE INTERVERTEBRAL DISCS IN A CHILD

Report of a Case Following Poliomyelitis

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CALCIFICATION of the intervertebral discs in childhood is said to be an infrequent occurrence. In a recent review, Silverman[1] collected eight cases from the literature[2-9] and added seven of his own.

Although calcification of the intervertebral discs in adult life is commonly associated with aging, sporadic reports of disc calcification with systemic or local complaints have appeared.[4, 10-12] In children, Weens[2] collected five such cases from the literature[5-9] and added one of his own. Cohen and associates[3] reported a similar case in a child with symptoms referable to the area involved roentgenologically. Only two of Silverman's seven cases had suggestive associated clinical findings.

The case reported herein is that of a 2½-year-old white female child in whom thoracic disc calcification was first noted one and one-half years following an attack of paralytic poliomyelitis. Of interest is the absence of intervertebral disc calcification at any level in the patient's monozygotic twin.

CASE REPORT

L. M., a 29-month-old white female child, was born Jan. 28, 1952, as one of twins, both of which were delivered in breech presentation. The birth weight was 4 pounds 13 ounces. The immediate neonatal course was uneventful. At 3 months of age, she received superficial roentgen therapy to the left cheek and right arm, presumably for small hemangiomas. She is said to have contracted chicken pox at 3 months of age and rubella at 4 months. At 26 months, she contracted rubeola, without sequelae.

At 11 months of age, on Dec. 18, 1952, she developed fever, irritability, an anorexia. Three days later she was given a single injection of penicillin and improved slightly; however, on December 25 she complained of pain and difficulty in moving both legs, with persistent fever and irritability. A lumbar puncture was performed, which was said to be within normal limits. On the following day, however, her condition worsened and she was admitted to the Barksdale Air Force Base Hospital, Louisiana. At the time of admission, slight neck and back extensor spasm was noted, as well as inability to move the right leg. Marked weakness of the quadriceps, hamstring and gastrocnemius groups was noted. Laboratory examination revealed a hemoglobin of 7.9 grams per cent and an erythrocyte count of 2.9 million. The urine was normal. A lumbar puncture done on admission revealed a protein of 78.5 mg. per cent, but no cells.

During twelve days of hospitalization no fever was noted, but the child was quite irritable. A 200 c.c. whole blood transfusion was given with moderate symptomatic improvement. She was discharged to orthopedic care, which has been continuous to the present time. A pronounced atrophy of the right thigh and calf muscles was noted on discharge, as well as a

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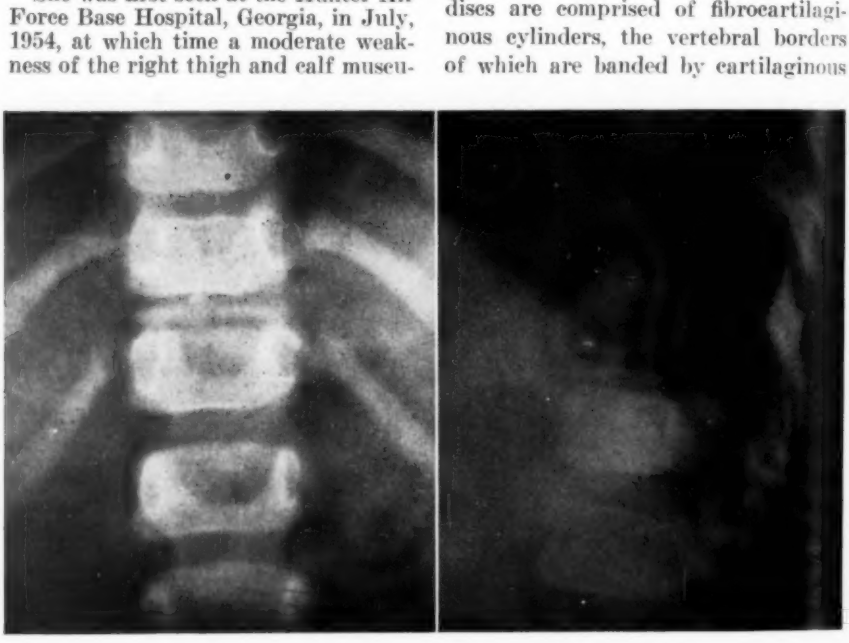
varus deformity of the right foot. After a short period on crutches, she was able to get about well with a knee-length brace, which has been shortened twice. It is of interest that an orthopedic film made in December, 1953, demonstrated a calcification at T_{11}-T_{12} but it was overlooked at that time.

She was first seen at the Hunter Air Force Base Hospital, Georgia, in July, 1954, at which time a moderate weakness of the right thigh and calf musculature was noted. Atrophy of the calf was prominent. She walked well with a brace and was otherwise a healthy, normal child of average intelligence. The right leg was 1.4 cm. shorter than the left on scanography. Radiographic examination of the spine was done to rule out the presence of scoliosis, and extensive calcification was noted at the T_{11}-T_{12} intervertebral disc space, with a faintly visible, possible second area at T_{12}-L_1 (Fig. 1). Six months later, the former area had increased slightly in extent but the latter had disappeared. Films of the patient's twin demonstrated no abnormality of the spine at any level. The urine was negative for homogentisic acid.



A. *B.*

Fig. 1.—Roentgenograms of thoracolumbar spine at 29 months of age. Considerable calcification is demonstrated in the intervertebral disc space between T_{11} and T_{12}. The calcification appears to involve both the annulus and nucleus. The margins of the vertebral segments are not remarkable.

ETIOLOGY OF INTERVERTEBRAL DISC CALCIFICATION

Anatomically, the intervertebral discs are comprised of fibrocartilaginous cylinders, the vertebral borders of which are banded by cartilaginous plates in early life. The nucleus pulposus accounts for approximately half the area of the disc.[13] The nucleus is composed of a mucoid substance containing an irregular latticework of fine collagenous fibers.[13-15] Enclosing the nucleus is the annulus fibrosus, which is demarcated from the nucleus by a transitional zone of collagenous fibers.[6] A second group of collagen fibers comprises the outer layer of the annulus

and also joins the vertebral surfaces above and below. The nucleus pulposus is thought by most authors to be an avascular structure.[13-15] Böhmig[16] purports to have demonstrated small vascular channels penetrating the cartilaginous plates in the first three decades of life.

Calcification of the intervertebral discs has been demonstrated at all ages microscopically, localized mainly to the annulus fibrosus in the first three decades.[14] These are thought to be secondary to calcium deposits in areas of traumatic rupture and subsequent necrosis. At all ages, calcification is more common in the annulus fibrosus.[4, 11, 14] Its greatest incidence topographically is in the mid-dorsal region.

Although intervertebral disc calcification is generally considered to be a degenerative process, this is an unlikely etiology in childhood. Aside from ochronosis, a known cause, various authors have proposed ischemic necrosis,[2] metastatic infectious processes,[7] and trauma.[17] Silverman[1] believes the origin to be unclear, but suggests that the majority are incidental findings, while transient cervical calcification associated with local symptoms may be a separate disease entity.

DISCUSSION

The case reported is the sixteenth case of intervertebral disc calcification reported in a child. It is the ninth case in which local symptoms and signs of a disease process referable to the area of roentgen involvement has been noted; in this instance the calcification followed an attack of poliomyelitis which has left fairly severe residuals in the right lower extremity. Although no proof can be given that the calcification did not antedate the paralytic disease, the suspicion is strong that a causal relationship exists. The appearance of the calcification suggests that it is localized in large part to the nucleus pulposus. Nuclear calcification has never been reported before the third decade in many large anatomical series, and is uncommon thereafter.[4, 11, 14] Sandström[18] believes that the tissue of which the nucleus is composed is similar to peritendinous tissue, in which impermanent calcification may occur elsewhere in the body. It would seem likely that calcification of the intervertebral disc in childhood is a separate disease entity, which is usually associated with locally referable symptoms and findings. Those cases in which it has been reported as an incidental finding have not been particularly normal individuals[1] but are those in whom, by reason of extensive medical study, such findings were statistically more likely to be noted. It is suggested that a local inflammatory process involving a segment of the spine may give rise to local necrosis and secondary permanent or transient calcium deposition in the intervertebral discs.

SUMMARY

A case of a 29-month-old white female child with roentgenologically demonstrable intervertebral disc calcification discovered after an attack of paralytic poliomyelitis is presented. Calcification was not present in the child's monozygotic twin.

The literature on the subject is reviewed.

The suggestion is made that calcification of the intervertebral discs in childhood is a separate entity related to a

definite type of disease process in childhood which involved the spine and perhaps the spinal cord.

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NEUROBLASTOMATOSIS IN ONE OF MONOZYGOTIC TWINS

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THE possibility of genetic disparities in monozygotic twins has been discussed previously,[1] particularly with regard to those disturbances which result from rotational (or torsional) aberrations.

It is true that neuroblastomas may arise from any site in which sympathetic nervous system tissue is present, but that site is preponderantly the medulla of the adrenal gland. Cells which had their origin in the primitive neural crest serve as the *anlage* for this malignancy.[2]

CASE REPORT

Twins James S. (birth weight 4 pounds 12 ounces) and John S. (the patient), whose birth weight was 4 pounds, 15 ounces, were born on May 6, 1951. There was a single placenta with two cords. Past illness had consisted of recurrent rhinitis and asthmatic bronchitis. Response to therapy with antibiotics had been good. An older sibling and James had both had surgical repair of inguinal hernias.

Both twins developed a respiratory infection during December, 1953, and responded to treatment with Ilotycin and Hydryllin compound. The cough recurred and a chest x-ray was made with the findings of early inflammatory process in the left central lung field of John. The paramediastinal density (early films) led to the impression of aortic anomaly, though one radiologist suggested that this might represent a large lymph node. A chest x-ray taken of James was found to be normal.

John was admitted to the St. Francis Hospital on Feb. 23, 1954, at which time he presented a markedly asthenic appearance. The eyelids were edematous, and small purpuric areas were present. The skin was pale, and minimal generalized adenopathy was present. Neither splenic nor hepatic enlargement was noted.

The hemoglobin was 43 per cent; the red blood count 2.8 million and the white blood count 6,700 per cubic millimeter of blood. There were 61 polymorphonuclears, 33 lymphocytes, 2 eosinophils, and 4 monocytes. The urine was normal; and the tuberculin and histoplasmin tests were negative.

The temperature curve was normal. Treatment consisted of 250 c.c. of whole blood intravenously. Erythrocin was given every six hours in dosage of 100 mg. A repeated count showed the hemoglobin was now 73 per cent, the red blood count 3.61 million and white blood count 8,750 for each cubic millimeter of blood. He was sent home on Feb. 26, 1954.

He was readmitted March 12, 1954, because of increasing weakness, fever, and abdominal pain. It was found that he now had a marked generalized adenopathy, hepatomegaly, and a large firm mass in the left upper quadrant. The hemoglobin was 56 per cent, the red blood count 3.4 million and the white blood count 7,500 for each cubic millimeter of blood. The differential count showed 15 per cent stabs, 22 per cent segmentals and 61 per cent lymphocytes. The platelets were normally abundant.

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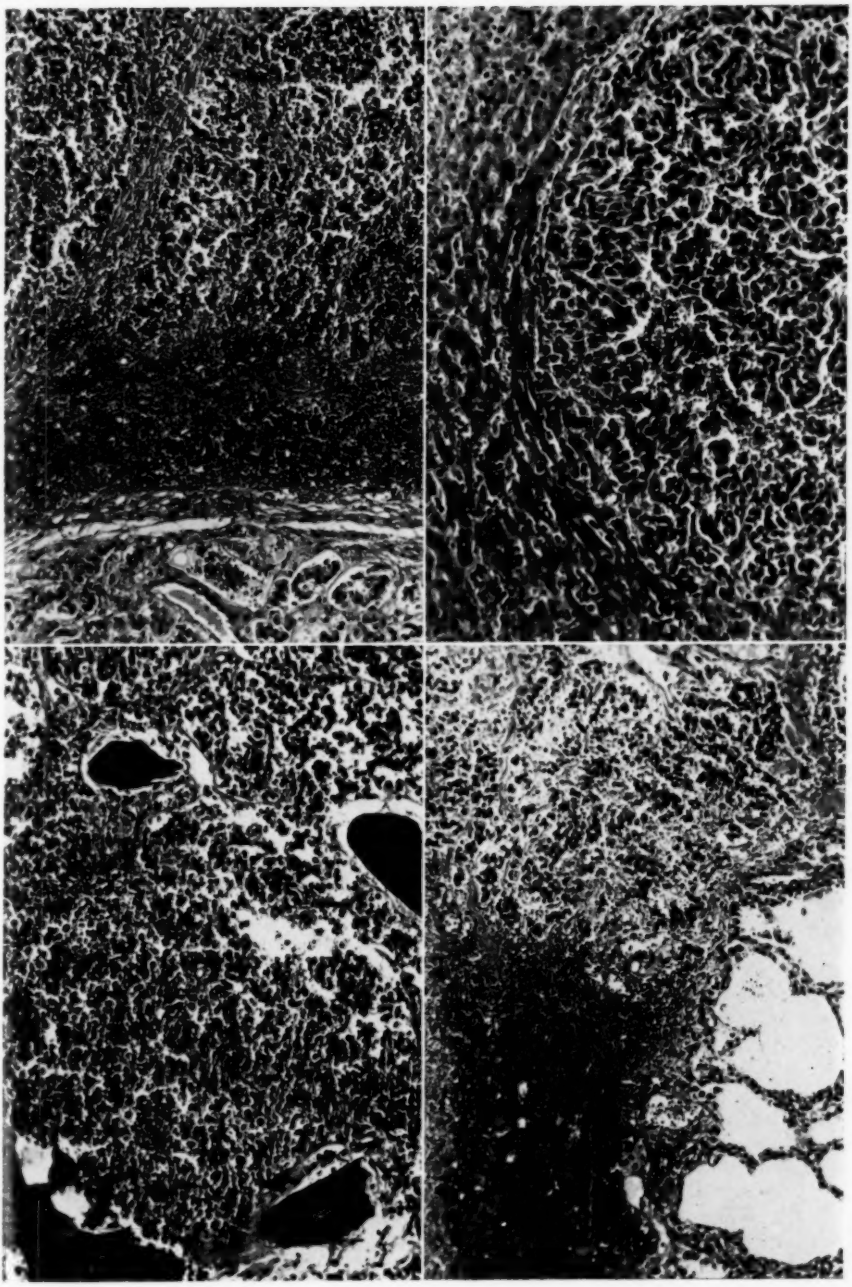
Pathological details interpreted and furnished by Drs. Harold C. Thornton and Joseph L. Haymond.

Aided by a grant from the Charles J. Wolf Foundation for Medical Research.

Fig. 1.—The patient, John (left), with his twin brother.

Fig. 2.—Chest x-ray of John, showing the huge hilar gland simulating an aortic anomaly.

Fig. 3.—Gross specimen: the large adrenal tumor (10 by 17 cm.).



B.

D.

Fig. 4.—*A*, Section of adrenal tumor showing a highly cellular undifferentiated structure. The cells show variation in size and shape. The nuclei are dark-staining, and a small amount of cytoplasm is present. Mitotic figures are fairly numerous in some areas. Capillaries are quite numerous. *B*, Numerous nodules of tumor tissue present in the liver. *C*, Extensive involvement of bone marrow by tumor tissue. *D*, Areas of tumor tissue in the lung. There are small clumps of tumor cells within the capillaries.

The chest x-ray was repeated and showed marked enlargement of the right paramediastinal density. Mottled areas of rarefaction were apparent in the proximal ends of the humeral shafts.

Bone marrow sample obtained revealed a highly cellular specimen, containing mostly large young cells, many of which were irregular in outline. The cytoplasm was deeply basophilic and, in some instances, vacuolated. Very few lymphocytes were noted and granulocytes and nucleated red cells were scarce. The platelets were markedly reduced in number. The findings were regarded as indicative of neuroblastoma.

The ocular changes were now marked in spite of supportive therapy. Pallor and weakness were rapidly progressive, and the child died on March 27, 1954.

The final anatomical diagnoses included:

1. Neuroblastoma with metastases to liver, lungs, lymph nodes, bone marrow, and pancreas.

2. Metastatic tumor nodule in upper mediastinum simulating an aortic anomaly by x-ray.

3. Myelophthisic anemia.

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AGENESIS OF ABDOMINAL MUSCULATURE WITH ECTOPIC URETERAL ORIFICE AND CONGENITAL ABSENCE OF OPPOSITE KIDNEY AND URETER

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DIABETES mellitus in the mother is known to be a predisposing factor to congenital abnormalities. The reported case demonstrates the benefit obtained from an early diagnosis of all the congenital defects and the institution of appropriate therapeutic measures. It further is an addition to the small but growing list of cases of agenesis of the abdominal musculature with associated defects in the genitourinary system.[1-11] This is the twelfth reported case of a living person in whom a diagnosis of ectopic ureteral opening into the seminal vesicle has been made and, to our knowledge, the first such patient with congenital absence of the opposite kidney and ureter.[12-19]

CASE REPORT

This male infant was delivered by cesarean section on Sept. 22, 1951, seven weeks prematurely, of a diabetic mother, following rupture of membranes accompanied by bleeding due to premature separation of the placenta. He weighed 5 pounds 4 ounces at birth. Respirations were spontaneous, but the cry was feeble. After one hour, the respiratory movements became less vigorous and edema began to appear. Physical examination at birth revealed a deformity of the thoracic cage on the left side with scoliosis involving the thoracic vertebrae, later found to consist of an incomplete ninth thoracic vertebra and spina bifida occulta of the third through the twelfth thoracic vertebrae (Fig. 1). There was apparent partial-to-complete absence of the musculature of the abdominal wall with bilateral complete inguinal hernias, umbilical hernia, and herniation of the spleen into the subcutaneous tissue with each respiratory movement (Fig. 1).

His hospital course was stormy, with clinical evidence of hyaline membrane disease, intracranial bleeding, jaundice, and edema. On the fourth day of life, he required artificial respiration for three hours before respiratory movements resumed. Under close nursing supervision, he received oxygen, antibiotic drugs, multiple small blood transfusions, adrenal cortex, and vitamin K. He was discharged on the twenty-second day of life. Growth and development were retarded during the first six months of life. Operation performed when the patient was 6 months old to correct the inguinal hernias was followed by uneventful recovery and cure.

When the general condition of the patient justified further diagnostic procedures, and despite the absence of any urinary symptoms, urologic consultation was requested because of the high incidence of anomalies of the urinary tract coexisting with agenesis of the abdominal musculature. Complete urologic examination, including urethroscopy, cystoscopy, and intravenous pyelography, revealed congenital absence of the left kidney and ureter

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(Fig. 2). Pronounced tortuosity, redundancy, and dilatation of the entire right ureter were observed, the distal end being considerably more dilated than the proximal end (Fig. 2). Urethroscopy demonstrated no apparent urethral abnormalities, although visualization was not too satisfactory because of the small size of the urethra. Cystoscopy revealed no evidence of a left ureteral orifice. A bulging mass in the area of the right ureteral orifice was considered to be a ureterocele, but no ureteral orifice could be identified. Indigo carmine was injected intravenously, and although dye could be seen in the bladder within about seven minutes, the point of entrance of the dye could not be determined.

A preoperative diagnosis of right ureterocele was made. Because the ureteral orifice could not be identified, transurethral approach was considered contraindicated. A suprapubic cystostomy was, therefore, performed on Jan. 7, 1953, at the age of 15 months, at which time the previously described mass was seen in the right floor of the bladder near the bladder neck. It did not have the typical appearance of ureterocele. Careful inspection again failed to reveal any evidence of ureteral orifice. Indigo carmine was injected intravenously, and about seven

Fig. 1.—Roentgenogram showing congenital malformations in a male infant delivered seven weeks prematurely of a diabetic mother: deformity of left thoracic cage, scoliosis involving thoracic vertebrae, incomplete ninth thoracic vertebra, spina bifida occulta of the third through the twelfth thoracic vertebrae, and complete absence of musculature of the left lateral abdominal wall. Note bulging defect of left flank caused by herniation of spleen into subcutaneous tissue with each respiratory movement.

Fig. 2.—Intravenous pyelogram taken preoperatively, showing congenital absence of left kidney and ureter, with tortuous, dilated, right ureter.

Fig. 3.—Intravenous pyelogram forty-eight days postoperatively. Note definite decrease in size of ureter.

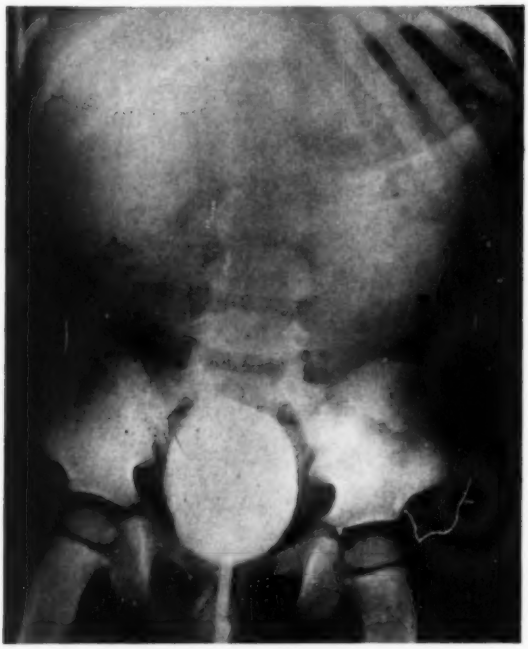

Fig. 4.—Retrograde cystogram twenty months postoperatively. No evidence of vesicoureteral reflux.

Fig. 5.—Intravenous pyelogram twenty months postoperatively. Note further decrease in size of ureter.

minutes later, dye was observed flowing intermittently from the urethra into the bladder. The diagnosis of ectopic ureteral orifice was then obvious.

The right perivesical space was exposed, and the ureter was identified. It was traced into a large, soft mass in the area of the right seminal vesicle. The vas deferens was identified and was traced to its point of entrance into this same mass, establishing the identity of this mass as dilated seminal vesicle into which the right ureter terminated. The right ureter was doubly clamped immediately proximal to the seminal vesicle and was divided, and the distal stump was ligated. The proximal stump was then implanted into the floor of the bladder as near the trigone area as possible. A No. 8 French polyvinyl catheter was then passed up the ureter and brought out through the anterior bladder wall with a cystostomy catheter. The postoperative course was uneventful. The ureteral catheter was removed on the fourth postoperative day, and the cystostomy catheter was removed on the ninth postoperative day. There was slight suprapubic urinary leakage for forty-eight hours after removal of the cystostomy catheter, after which the wound remained dry. The patient was discharged from the hospital on the eleventh postoperative day.

An intravenous pyelogram taken forty-eight days postoperatively showed a definite decrease in the size of the ureter (Fig. 3). Twenty months postoperatively, a retrograde cystogram demonstrated no evidence of vesicoureteral reflux (Fig. 4), and an intravenous pyelogram showed still further decrease in the size of the ureter (Fig. 5). The patient is completely asymptomatic at this time.

DISCUSSION

This report is presented to emphasize the importance of careful examination and observation for evidence of congenital anomalies in any child born of a diabetic mother. Complete urologic examination is imperative in every patient with a defect of the musculature of the abdominal wall because almost all of these patient have associated anomalies of the genitourinary tract. Although the most common abnormality of the urinary tract found to be associated with absence or deficiency of abdominal musculature has been obstruction of the vesical neck, all types of anomalies have been reported.[1, 5, 10]

Although the relationship between agenesis of abdominal musculature and anomalies of the urinary tract has been discussed extensively, the exact relationship remains unknown. Several theories have been advanced, all ably presented by Bruton,[1] Eagle and Barrett,[3] Culp and Flocks,[5] and Silverman and Huang.[10]

In reviewing the literature on this subject, we have been impressed by the fact that even when absence or deficiency of abdominal musculature was noted at birth, urologic examination was usually not requested until urinary symptoms occurred, often too late to correct an irreparably damaged urinary tract. We believe that complete urologic examination, including intravenous pyelography, retrograde cystography, urethroscopy, and cystoscopy, should be performed promptly.

In a review of the literature on ectopic ureteral opening into the seminal vesicle, the one striking feature of all reports was the cystoscopic finding of an elevation, or bulging globular mass, on the side of the trigone affected. With such an observation, differentiation between ureterocele and ectopic ureteral opening into the sem-

inal vesicle is sometimes difficult to make by visualization alone, and the possibility of the latter should, therefore, always be kept in mind by the cystoscopist. The embryologic origin of this type of anomaly has been clearly explained by Campbell.[20]

SUMMARY

A case is reported of agenesis of the abdominal musculature, with ectopic ureteral opening into the seminal vesicle, in a male infant delivered of a diabetic mother. It represents the twelfth reported case of ectopic ureteral opening into the seminal vesicle and, to our knowledge, the first such case with congenital absence of the opposite kidney and ureter. Bilateral complete inguinal hernias, umbilical hernia, and herniation of the spleen into the subcutaneous tissue with each respiratory movement were also observed on physical examination at the time of birth. Despite absence of urinary symptoms, complete urologic examination was performed as soon as the general condition of the patient permitted. Following urethroscopy, cystoscopy, and intravenous pyelography, a suprapubic cystostomy was performed, and an operative diagnosis of ectopic ureteral orifice was made. The postoperative course was uneventful, and follow-up urologic examinations have revealed continued improvement of the right urinary tract. The patient is asymptomatic at this time.

All patients with defect of the musculature of the abdominal wall should have complete urologic examination, regardless of the absence of symptoms, as there is a high probability that associated genitourinary anomalies are present. Early examination, with prompt institution of corrective measures, may prevent irreparable damage to the urinary tract and permit normal function.

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A Tale of Woe

July 29, 1773. . . . Would have carryed my Daughter (Mrs.) Baldwin to Southborough, but She was too poorly—vomiting a great many times. Hannah rode with me, in my Daughter's Chaise. . . August 1. . . My Dauter Baldwin is in a weak, low & distressed Condition frequently vomiting. Dr. Howes visits her & administers to her such physick as may clear her Stomach. . . . August 6 My Dauter is Somewhat better yesterday & to Day. August 16. My Dauter Baldwin is so much better & so desirous to return to Brookfield. August 23. my daughter Hannah very poorly. Dr. Hawes with her. August 25 Hannah is very poorly to Day: cant Keep off from ye Bed. Elias also not well. The Dr visits & administers but Hannah is no better. August 27 Elias as well as Hannah Still laid by. Can't but wish for Mrs Parkman's return. At Eve came my Wife & Dauter in law Kezia but Mrs. Parkman was much indisposed, and has been ever since she has been gone. August 28. my Family are much indisposed. My wife poorly; Hannah is ill; the Jaundice appears evidently; her Stomach much disorder'd. The Dr. has given her a vomit, which works as expected. Elias is exercised very much with pain—is capable of very little. September 2 My Wife is still worse, the Dr visits her. Hannah, thro divine Compassion better, So is Elias; but does very little at his Books. September 8 Mrs Parkman remaining poorly still, & my Daut. Hannah not firm. September 10. Sophy droops. September 13 Sophy is laid by with Sickness.

FROM EBENEZER PARKMAN'S DIARY.

THE TREATMENT OF ECZEMA IN INFANTS AND CHILDREN

PART III

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SECONDARY INFECTION

IT IS not uncommon, particularly in children, for any eczema to become secondarily infected. The Staphylococcus aureus and the beta hemolytic streptococcus are the most common organisms. Infection is manifested by pustules, which may be few or many, and which occur on the normal as well as on the eczematous skin. Such infection is now, as a rule, more easily cured than is the original eczema. Although it is true that many strains of staphylococcus are resistant to penicillin in vitro, it has seemed to me that this almost always works well against secondary skin infection, no matter if the infecting organism be a staphylococcus or a streptococcus. Furthermore, it works when given by mouth, and large doses are not necessary. I have usually given 300,000 units a day to a baby and 400,000 to a child: the soluble tablets to a baby, and buffered tablets to a child. It is well to continue the penicillin for about a week after the pustules have gone, in order to prevent recurrence. Theoretically, the broad spectrum antibiotics should work better—practically speaking, I doubt if they do.

For local treatment of large exudative areas of infection, wet dressings of potassium permanganate solution 1 to 8,000 are used: for smaller areas, where not much of the active drug will be absorbed, wet dressings of 0.25 per cent silver nitrate solution. For small, slightly oozing, impetiginous spots, or oozy broken pustules, I have always had good results with Alulotion* sopped on frequently. This is a colloidal ammoniated mercury preparation with kaolin and aluminum hydroxide gel. In addition to its strong antiseptic action it is also astringent—it dries up and shrinks small, wet lesions. For large areas that are not exudative I have used neomycin, bacitracin, or "Erythro-Myciguent"† ointments. All of them are good—I have been unable to see that one is any better than the other.

Fresh underclothes should be worn every day and boiled before washing, the fingernails should be kept short and scrubbed two or three times a day, as the spread of secondary infection is largely brought about by autoinoculation from scratching. Ammoniated mercury ointment (3 per cent) is still a good skin antiseptic, and I suspect that the greatly improved results in the treatment of

Editor's Note: Despite the notice in the August issue that reprints would not be available of Dr. Hill's series of papers on "The Treatment of Eczema in Infants and Children," many requests are being received. As previously stated, no reprints are available as the articles will be published in book form.

*Wyeth Incorporated, Philadelphia.
†The Upjohn Co., Kalamazoo, Mich.

skin infection in recent years are due more to the internal administration of the antibiotic than to great superiority of any one of them over ammoniated mercury when applied locally.

Infectious Eczematoid Dermatitis (Bacterial Eczema, Infective Eczema)

There is a distinction between secondarily infected eczema and bacterial eczema. In the former, the eczema is not caused by bacteria; it simply has bacterial infection engrafted upon it—in the latter, low-grade bacterial infection usually without pustulation and often bacterial sensitization as well are contributory or even primary causes of the eczema. Originally by "infectious eczematoid dermatitis" was meant an eczema caused by the irritating effects on the skin of a purulent discharge from such a focus as a chronic otitis media, a draining sinus, or a boil. In pediatric practice before the days of antibiotics this used to be fairly common in children whose ears ran all winter, as they often did.

In the last few years this conception of bacterial eczema has been somewhat broadened. It is recognized that many eczemas which show no gross evidence of infection are kept active by low-grade infection and by allergic sensitivity to the infecting organism, and that treatment must be combined antieczematous and antibacterial. Cultures are of little use in diagnosis, for the organisms which cause the trouble are, as a rule, the same which can be recovered from normal skins (*Staph. aureus* and occasionally beta hemolytic streptococcus). Although the bacterial flora of the eczema lesions is not likely to be any different qualitatively from that of the normal skin, it is very different quantitatively; the number of bacteria is enormously greater. This has been especially emphasized by Storck.[5] And what is even more important, he obtained positive patch tests in many patients with suspensions of bacteria recovered from their own eczema lesions. Bacterial eczema is likely to be chronic, thickened, often somewhat oozy and crusted in acute exacerbations, and usually rather sharply circumscribed. It is common behind the ears in combination with localized seborrheic dermatitis of the scalp, and on the face and backs of the hands in infants, although it may occur on any part of the body. The eczematous skin is a skin with diminished resistance, and the products of inflammation make excellent culture media for bacteria; it seems likely that they may play a part in almost any fairly deep-seated moist and crusted eczema.

The treatment of bacterial eczema is a combination of treatment directed against the eczema and against infection (see atopic dermatitis). Antibiotics given internally are often worth while, but they are not likely to accomplish as much as they do in secondarily infected eczema with pustulation. Antieczematous and antibacterial local treatment is likely to do more good, but it is very difficult to get rid of bacteria in a deep-seated patch of eczema. Staphylococcus toxoid and vaccine have been highly recommended by some—others say they are of little value. I have

[5]Storck, Hans: Experimentelle Untersuchung zur Frage der Bedeutung vom Microben in der Ekzemgenese, Dermatologica 96: 177, 1948.

not had enough experience with either to be able to express an opinion that would mean anything.

The boy shown in Fig. 14 was about 3 years old. The large areas on his cheeks began as small "spots" when he was about 2 years old and gradually spread. There was never any eczema anywhere else on his body. The cheeks had been treated with many ointments and lotions, without result. Neomycin ointment produced remarkable improvement in a short time.

Fig. 14.—Infectious eczematoid dermatitis in a child of 3 years. Ordinary atopic dermatitis is uncommon on the face at this age.

I think it is probably true that almost all oozy and crusted eczemas of the scalp and face with much detritus in young babies, even if they are not ordinarily classed as bacterial eczema, are aggravated by bacterial infection, and it is a good plan to give penicillin orally as a routine to such patients for a short time, and to continue it if it has produced good results.

Nummular Eczema

Some dermatologists classify nummular eczema as infectious eczematoid dermatitis, some group it by itself. For the present, I prefer to group it by itself.

Nummular eczema is not uncommon in children after the first year; I have rarely seen it before this. It appears as circular coin-sized (nummular) patches on the extremities, trunk, and face. These patches may be few or many, and it is common for several to coalesce and to form sheetlike areas, especially on the lower legs. The skin between the patches is normal in appearance. I have never seen erythroderma in nummular eczema. Each patch is made up of many small vesicles, which rupture easily, ooze a little, and crust. The larger areas especially are considerably thickened and "boggy," and of a deep purplish-red color. Itching is variable: sometimes very little, sometimes a lot. In addition to the nummular patches there is in many patients* what appears to be ordinary atopic dermatitis on the face, neck, and sometimes on the legs. Nummular eczema may occur in children with strongly positive skin tests, especially to egg white, or in children with entirely negative skin tests in whom no allergy can be demonstrated. Like some of the "fixed" drug eruptions it tends to recur in exactly the same places where it was in the beginning.

The cause is unknown, although there is some evidence to indicate

*I am talking about babies and children only.

that a partial cause may in some cases be a low-grade infection with staphylococcus plus sensitization to the infecting organism. This view is held by Fowle and Rice.[6] By an ingenious method of plate culture similar to that employed by Storck, they demonstrated clearly that plaques of nummular eczema contained an enormously greater number of staphylococci than on the normal skin, and they reported good results with staphylococcus toxoid and vaccine. It is clinically true that flare-ups are often seen in children who have nummular eczema, when they develop a nasopharyngeal infection or a tonsillitis, and that some can be cured by removal of tonsils and adenoids. Such foci of infection are found by no means in all of these patients, however.

Fig. 15.—Nummular eczema.

Children with nummular eczema can be helped a great deal by proper treatment, but recurrences are common. I have never seen the removal of any food or environmental allergen do any good. It is probably best, however, if there are positive skin tests to foods, such as egg white, to withhold the corresponding foods from the diet. This will have no effect upon the "nummular" lesions, but it may help the ordinary eczema which so commonly goes along with them. Furthermore, some of these children are so sensitive to egg white that they can eat none of it without severe and immediate symptoms such as vomiting, urticaria, or even shock—entirely apart from what the eating of egg might or might not do to the eczema. If there is a focus of infection in the nose or throat (purulent nasal discharge or infected tonsils), the use of an antibiotic will probably get rid of it, and when this happens, the eczema is likely to be greatly improved. I have seen one prompt and spectacular cure of a nummular eczema by the use of penicillin nose drops and penicillin internally for a boy who had a profuse purulent nasal discharge. If no focus of infection can be found I doubt that antibiotics do any good. Antibac-

[6]Fowle, L. P., and Rice, J. W.: Etiology of Nummular Eczema, Arch. Dermat. & Syph. 68: 69, 1953.

terial treatment of the lesions accomplishes but little; one would expect that if they were actually caused by bacteria, treatment with ammoniated mercury or antibiotic ointments would cure them: it does not. Vioform sometimes does fairly well; whether due to its antiseptic action or something else I do not know, but in my experience the only local treatment that really amounts to much is the use of crude tar, full strength, painted on each lesion twice a day. It is allowed to dry a little, then powdered with talc.

Fig. 16.—Nummular eczema. Local treatment: smaller lesions to be painted with undiluted crude coal tar. Larger lesions to be treated with a strong tar paste. No greasy, thin ointments to be used. (From Brennemann's Practice of Pediatrics.)

If there are large patches it is best not to paint them all at once, but to get rid of a few at a time and then go on to the others. Results with this

treatment are sometimes spectacular, and I have seen in some cases complete disappearance of the smaller patches in a few days. The large, purplish, boggy plaques on the legs are more

Fig. 17.—Nummular eczema. Note ordinary eczema on legs and neck.

difficult, and progress is slow. For such places a thick tar paste does well (see atopic dermatitis). Greasy ointments should not be used. The ordinary eczema which may be present around the neck and on the face is helped by hydrocortisone ointment if not much thickened; if thickened, tar paste is better. (See Fig. 17.) This child was treated with hydrocortisone ointment to the face and neck, crude coal tar to the small places on the body, and tar paste to the legs plus bandages.

I cannot emphasize too strongly the superiority of coal tar for nummular

Fig. 18.—Nummular eczema. (From New England J. Med., 1953.)

eczema over anything else that I have used; treatment must be persistent, however.

I have treated several patients who had nummular eczema with cortisone by mouth, and have come to the con-

clusion that it is no good. In ordinary dosage (75 mg. per day) it accomplishes very little, and I do not recommend the use of larger doses for children with eczema. The boy in Fig. 18 was treated with oral cortisone, 50 to 75 mg. doses for a long time without much effect, except to diminish the oozing. Once when he was in a hospital the resident gave him 150 mg. for a day or two. The eczema

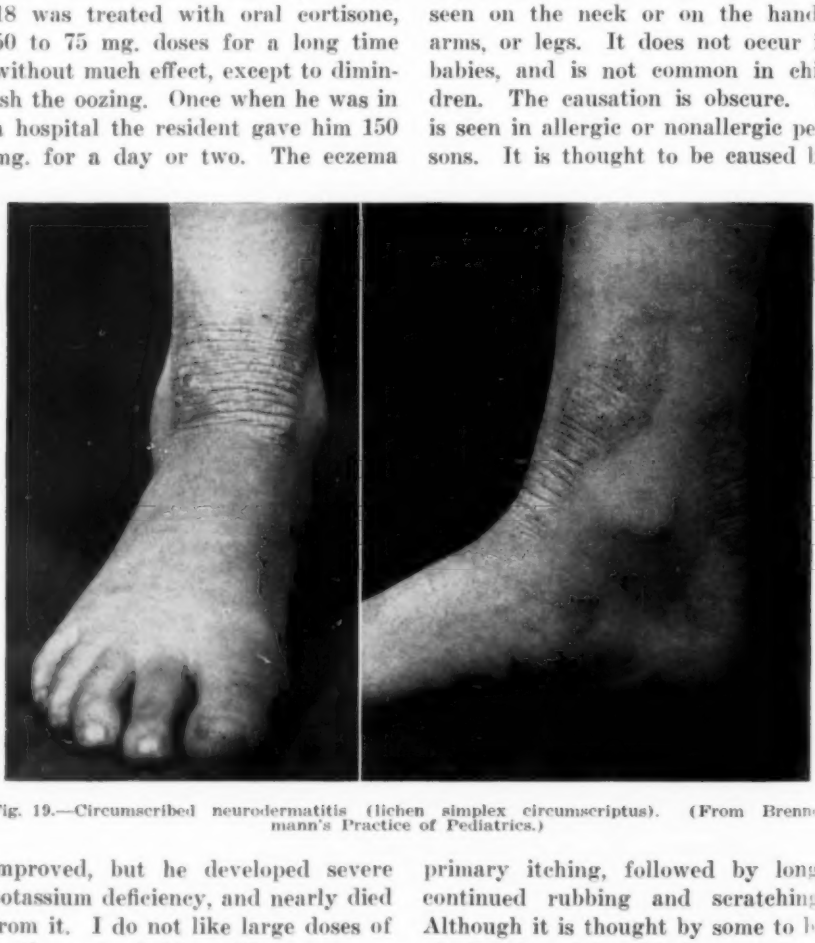

Fig. 19.—Circumscribed neurodermatitis (lichen simplex circumscriptus). (From Brennemann's Practice of Pediatrics.)

improved, but he developed severe potassium deficiency, and nearly died from it. I do not like large doses of cortisone for babies with eczema.

Circumscribed Neurodermatitis (Lichen Simplex Circumscriptus)

By circumscribed neurodermatitis is meant one or several irregularly shaped, usually small, and much thickened itchy patches which have become lichenified; they look like the skin of a rhinoceros. There is a sharply defined separation between the patch and the healthy skin. Circumscribed neurodermatitis is usually seen on the neck or on the hands, arms, or legs. It does not occur in babies, and is not common in children. The causation is obscure. It is seen in allergic or nonallergic persons. It is thought to be caused by primary itching, followed by long-continued rubbing and scratching. Although it is thought by some to be of allergic origin, this has not been proved, and the removal of foods or other allergens from the diet does no good.

The best treatment is the *persistent* use of a strong tar ointment with the addition of salicylic acid, well rubbed in.

℞ Acid salicylic ʒ ss
Crude coal tar ʒ ii
Hydrophilic ointment (U.S.P.) ℥ ii

Contact Dermatitis*

I am writing especially for pediatricians. I will therefore start this section by suggesting to them that it would be best if they discarded the idea that all eczematous skin eruptions in infants and children are caused by what they eat and cured by removing some food from the diet.

Contact dermatitis is the most common eczema of adults. It is not so common in infants and children because they are not exposed to the multiplicity of skin sensitizers that adults are. In 156 consecutive cases of eczema from my office records, in patients between the ages of 1 and 17 years, I made the diagnosis of contact eczema thirty-one times. I have no figures for young babies. I doubt if the percentage would be so high; however, it is common enough so that the possibility of it should always be borne in mind.

Contact dermatitis may be caused by irritation of the skin by substances which cause irritation in all persons (primary irritants) or by substances which irritate only when the patient has become allergically sensitized to them. The epidermis is the seat of sensitization—there are, so far as is known, no circulating antibodies, no hereditary predisposition as there is in atopic dermatitis, and no association, except fortuitously, with asthma or hay fever. Contact dermatitis is an episode, atopic dermatitis a disease; the episode is not uncommonly superimposed upon the disease and a contact dermatitis may be added to an existing atopic dermatitis. I think it is probable that those who have atopic dermatitis are somewhat more likely to develop contact dermatitis than are those who do not have it. Not all would agree with this.

The causes are innumerable: metals, dyes, essential oils, plastics, cosmetics, turpentine, plant oils, drugs—indeed, chemicals of almost any sort, organic or inorganic, which come into contact with the skin.

The most important things in the treatment of contact dermatitis are:

(1) To be on the lookout for it, and to realize that it occurs at any age. To decide whether or not you are dealing with a contact dermatitis.

(2) To get at the cause, if possible, and remove it.

(3) To keep the skin entirely protected from contact with anything which might do it harm.

(4) Local treatment with various lotions, pastes, or ointments: the same as for atopic dermatitis. (See atopic dermatitis.)

The appearance of the skin in acute contact dermatitis varies all the way from simple erythema, with slight scaling, to the most intense vesiculation, or even bullae. If such eczema appears rather suddenly on a previously healthy skin, particularly if it appears in one place on an exposed surface, contact dermatitis should always be considered. In chronic cases there is a good deal of thickening and even lichenification, so that the appearance may closely resemble that of atopic dermatitis. The borders are not sharp, and the trouble may, in a short time, spread from the point of original contact, sometimes by transfer with the fingers, probably sometimes through the blood stream. It is usually not hard to be reasonably

*I have used the words "eczema" and "dermatitis" interchangeably.

Fig. 20.—Contact dermatitis from Metaphen nose drops. Patch test to mercury strongly positive. (From Brennemann's Practice of Pediatrics.)

Fig. 21.—Contact dermatitis from ammoniated mercury ointment. Local treatment: zinc oxide paste (U.S.P.). (From Brennemann's Practice of Pediatrics.)

sure from the history and from the appearance and location of the eruption that a contact eczema is present, but determination of the cause is quite another matter. All too commonly it is never determined. I have done a great many patch tests in children when I *knew* that the eczema was of external origin, and have seen few positive tests. I think the probable reason is that in many of these children the degree of sensitization is not great enough to cause dermatitis unless the contact is prolonged and there is a certain amount of trauma of the skin as well (rubbing). The extreme degree of sensitivity that is so often seen in adults is not so commonly seen in children, although I see no reason why, if they were sensitized to some of the things that cause so much trouble in adults (such as paraphenylenediamine or various metallic salts), they should not give as well-marked patch tests as the adults do. The children shown in Figs. 20 and 21, who were sensitive to mercury, gave well-marked positive patch tests.

Some of the things to suspect are as follows: "baby oils," most of which contain essential oils (aromatic amines), salves or lotions which have been used in treatment, toilet water or other cosmetics, shampoos, turpentine, detergents or bleaching powders, dyes or "finishers" in clothes (very important), plastics, lacquered toilet seats, plants, and toys. I have never seen contact dermatitis from soap,* although it undoubtedly does occur. I have seen proved contact dermatitis in children from the following things: dyes, mother's cosmetics, primrose, ivy, the leaves of the white mulberry bush, plastics, toilet seat lacquer, ammoniated mercury, tar, sulfur, Sopronol, a proprietary shampoo, furniture polish, hair tonic, turpentine, creosote, and tincture of green soap.

*Except from tincture of green soap, due to the lavendar it contains.

Special Forms of Contact Dermatitis

Plant Dermatitis

In some parts of the country, dermatitis from weeds,[7] particularly ragweed, is common in adults; it is not common in children. The dermatitis is caused by contact with the oil contained in the leaves, stems, and pollen. Patch tests are positive. Eczema from pollen is common in children, but this is of the atopic variety, and is caused by inhalation of the pollen. Patch tests are negative, scratch or intracutaneous tests are positive, with the protein fraction of the pollen. Ordinary "poison ivy" is, of course, common in children almost everywhere.

Treatment of Poison Ivy

1. *Prophylactic.*—There is much in the literature about this; some think that it is worthless, some that it is of great value. I have not had enough experience with prophylactic treatment for poison ivy to form any worth-while conclusions. From what little I have seen, from what I have read, and from the information gathered by word of mouth from others who have used it more than I, it would seem that it is worth while, but not reliable. It can be done by inoculation or by ingestion. Which is the better of the two methods, I do not know.

[7]Shelmire, Bedford: Contact Dermatitis From Weeds: Patch Tests With Their Oleo Resins, J. A. M. A. 113: 1085, 1939.

a. *Inoculation:* "Ivyol"*: 0.5 c.c. is injected intramuscularly for four weeks before the start of the ivy season.

b. *Ingestion:* "Rhus Tox"†: Start in the late spring with 5 drops three times a day in half a glass of water; increase 3 drops each day up to 15 drops three times a day. Give this dose every day all summer.‡

2. *Local Treatment.*—Poison ivy dermatitis is a self-limited disorder; it will get well, however, by itself if you do not try to do too much to it. In its more severe forms, however, it is what I would call a "very bad disease," and may require a good deal of treatment.

a. Under no circumstances give any inoculation with poison ivy extract. This is likely to do more harm than good if given when ivy dermatitis is present.

b. If the dermatitis is oozy, use wet dressings of 1 to 10,000 potassium permanganate solution, or Burow's solution, 1 tablespoonful to a glass of water.

c. If not oozy, apply the following lotion several times a day:

℞ Acid carbolic gr. xx
Zinc oxide ʒ ss
Lime water ʒ viii

d. After the acute stage has passed, use Lassar's paste for a few days—then a mild salve such as zinc oxide ointment (U.S.P.) or Acid Mantle Creme.§

e. If there is much itching at night, give chloral hydrate,‖ or Nembutal or Seconal.

f. In severe cases use cortisone by mouth, 100 mg. a day to children over 6 years, 75 mg. a day to those under 6 years, until the worst is over, then gradually reduce the dose and soon discontinue it.

*Sharp & Dohme, Philadelphia.
†The National Drug Co., Philadelphia.
‡If there is any burning or itching about the rectum, the dose should be reduced.
§Dome Chemicals Inc., New York.
‖Squibb's.

Contact Dermatitis From Clothing

I am inclined to think that in children the clothing is the most common cause of contact dermatitis. It may be difficult or impossible, however, to determine what constituent of, or additive to, the cloth is causing the trouble. Wool is a common cause of eczema—it can work either by inhalation or by contact. Such eczema is best classed under atopic dermatitis. (See atopic dermatitis.) Many dyes can cause contact eczema, and I have been pretty sure many times that the dye in clothes was causing the trouble, but have obtained few positive patch tests to the dyed fabric. Cotton cloth, when nothing has been added to it, is not allergenic. However, practically all cotton garments have had "finishes" applied to them as mordants, for softening or for stiffening, or for making the material look or feel better. There are a large number of these "finishes," of different chemical composition. The most common are starches, gums, resins, detergents, and bleaching agents. If eczema appears on the trunk after wearing a new undershirt, or on the upper legs or buttocks after wearing new shorts, it is likely that the cause may be one of these cotton "finishes."

Shoe Dermatitis[5]

Contact dermatitis from shoes is not uncommon and is often wrongly thought to be a fungus infection. It is caused more often from the cements,

[5]Glaul, L. Edward, and Underwood, G. B.: Arch. Dermat. & Syph. 60: 649, 1949.

asphalts, or other adhesives that are used in the linings of shoes than from anything to do with the leather itself. It is usually seen on the upper surface of the foot and toes, and not between the toes, which are protected from contact with the causative chemical. Fungus infection is likely to occur between and underneath the toes. When there is contact dermatitis from shoes it is quite a problem to know what kind of shoes to wear. Inasmuch as the trouble usually comes from various parts of the lining, unlined shoes of the moccasin "loafer" type or

Fig. 22.—Contact dermatitis from shoe linings, probably from the cement. Local treatment: zinc oxide paste, followed by Swartz's ointment or medium strength tar paste. (From Brennemann's Practice of Pediatrics.)

sandals made entirely of leather are the best shoes to wear. If the trouble is coming from the leather, sneakers can be worn. It is also quite possible that one pair of shoes will cause dermatitis, and another will not.

AMMONIA DERMATITIS

Ammonia dermatitis is common in babies of the diaper age and is caused by the breaking down into ammonia of the urea in the urine on the diaper by bacteria from the bowel. Ammonia dermatitis is a classical example of dermatitis from a primary irritant—there is no allergic sensitization. There may be erythema with moderate peeling, papules, bullae, or actual ulceration, depending upon the concentration of ammonia which contacts the skin. There is always in the diffuse erythematous type a sharp line of demarcation following the line of the diaper. The diagnosis is made by the appearance and by the strong ammonia smell, particularly in the morning, after the baby has had his wet diapers on all night.

I recommend that all young pediatricians read Cooke's[9] original paper in which he showed the cause of the trouble and recommended the first satisfactory treatment for it. He suggested that the diapers be soaked in mercuric chloride or in boric acid solution. The first works practically every time, the second is not much good. The diapers are washed and rinsed as usual, then soaked for an hour in a white enamel bucket three-fourths full of water in which one 7.3 grain tablet of mercuric chloride has been dissolved; then they are wrung out and allowed to dry without rinsing. This is the best treatment for ammonia dermatitis: I do not think any of the newer antiseptics that have been recommended are nearly as good. In the last few years it has been shown that most children with acrodynia have been exposed to mercury, and two cases have been reported following the use of mercuric

[9]Cooke, J. V.: Etiology and Treatment of Ammonia Dermatitis of the Gluteal Region in Infants, Am. J. Dis. Child. 22: 481, 1921.

chloride as a diaper disinfectant.[10] This must be very unusual, because for a long time most pediatricians have used Cooke's method, and acrodynia, in New England at any rate, is a rare disease. I have used this treatment for thirty-four years, since Cooke's original paper was published, for every baby that I have seen with ammonia dermatitis. There has been no acrodynia, no other child in the family has eaten the mercury tablets, and practically every patient treated has been cured entirely and completely.

DRUG DERMATITIS

Sensitization and ensuing dermatitis from drugs contained in local applications to the skin are very common in adults—I doubt if they are as common in infants and children. I have used coal tar for literally thousands of patients and ammoniated mercury in hundreds, and have seen just three cases of sensitization to tar and two to mercury. However, the indiscriminate use of all sorts of salves, often bought "over the counter" without prescription and without having any idea of what they contain, is to be condemned. If one is fearful that a child may be sensitive to some drug, it is a simple matter to do a patch test with it before using it on the eczema. Some of the more common sensitizing drugs are mercury, resorcin, sulfur, benzocaine, various proprietary "antifungus" preparations, salicylic acid, essential oils (used in some proprietary salves to make them smell better), penicillin, and sulfadiazine.

SUMMARY OF TREATMENT OF CONTACT DERMATITIS

It is important to have contact dermatitis in mind. If you do have it in mind you will see a good many children in whom you are reasonably sure that the trouble has been coming from the outside. Determination of the exact cause is, however, a very different matter, and often is impossible. The general principle of treatment, therefore, is to keep the skins of these children covered up, and in contact with nothing, if possible, except old white cotton cloth. This is never allergenic. The local treatment is the same as for atopic dermatitis. (See atopic dermatitis.)

(To be continued)

[10] McCoy, G. E.: Acrodynia Following the Use of Bichloride of Mercury as a Diaper Rinse. Report of 2 Cases, J. Indiana M. A. 43: 1095, 1950.

Physiologic Aspects of Pediatrics

HYPOPHOSPHATASIA—A NEWLY RECOGNIZED DISEASE

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A RECENTLY recognized disease of bone affecting infants, children, and adults, and with a specific deficiency of alkaline phosphatase, affords a unique opportunity to study the effects of this well-known enzyme. The disease is hypophosphatasia, first described by Rathbun[1] in 1948. Several subsequent reports[2-7] of additional cases suggest that the disease is not excessively rare and has been overlooked.

Hypophosphatasia is characterized by rickets and diminished alkaline phosphatase activity; this combination does not exist in any other recognized condition. Rathbun's original case was a 3-week-old male infant with presenting complaints of failure to gain weight and apparent pain on handling. Rachitic bone lesions were already well developed in this young infant, and diminished serum alkaline phosphatase activity persisted through six weeks of hospitalization despite vitamin D therapy and trials of thyroid and testosterone. While under treatment with testosterone, the infant died unexpectedly in a convulsive seizure. At autopsy, diminished alkaline phosphatase activity was demonstrated in tissues; and the bone lesions were pathologically indistinguishable from those of vitamin D deficiency rickets. Subsequently several other cases[2-7] have been described in infants and adults of both sexes. Some relatives of recognized cases also have the disease, and others have shown subnormal levels of alkaline phosphatase activity without bone lesions. An unusual symptom in hypophosphatasia patients is the premature loss of teeth, which occurred in several children described by Sobel and co-workers.[3] Schlesinger[7] reports premature closure of the cranial sutures, with craniostenosis and blindness. Deformities and dwarfing are common. Laboratory findings have not been strikingly abnormal except for uniformly diminished alkaline phosphatase activity and for elevation of the serum calcium in many but not all cases; serum phosphorus levels, which are normally higher in children than in adults, have usually been within normal limits, but were regarded as elevated at values of 6 mg. per cent in two patients[2] in whom excessive tubular resorption of phosphate was demonstrated. Severe renal lesions such as those found in "renal rickets" have not occurred, though slight elevation of the nonprotein nitrogen was found in Rathbun's case and some renal calcification at autopsy in another. De-

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pression of renal function secondary to persistent hypercalcemia is generally regarded as a hazard of the disease. No therapy has been successful. Trials of vitamins C and D, thyroid, testosterone, growth hormone, thiamine and Benemid have been reported; improvement in two patients treated with the last of these was claimed.[2] The use of testosterone seems unadvisable since it causes a reduction in kidney alkaline phosphatase activity in experimental animals. Some infants have died with the disease, but at least one[3] has grown at a normal rate in spite of progressive rachitic deformities. The presence of hypophosphatasia in adults indicates that either prolonged survival with the disease or its late appearance can occur.

This disease should help answer some of the questions regarding the function of alkaline phosphatase, which is one of the first recognized and most commonly measured enzymes in the body. Alkaline phosphatase activity is normally found in practically every tissue, but notably in calcifying bone, intestinal mucosa, kidney cortex, and lactating breast tissue. The enzyme is capable of splitting phosphate monoesters to yield inorganic phosphate, and is maximally active at an alkaline pH. Its function in most tissues is not definitely known, but a close relationship to bone disease and calcification has been recognized since 1923. In that year Robison[9] showed that when bone fragments rich in phosphatase acted on a suitable phosphate monoester in vitro, inorganic phosphate was liberated and a precipitate of calcium phosphate was formed. The possible importance of this mechanism for in vivo calcification of bone was apparent. Robison believed that enzyme action produced sufficient inorganic phosphate to exceed locally the solubility product of calcium and phosphate, which are normally carried almost at saturation in serum, and a precipitation of bone salt followed. Some such mechanism undoubtedly operates, but many details are not clear. The osteoblasts, or bone-forming cells, are normally rich in alkaline phosphatase; during bone growth or repair their number and activity are increased, and the increase is reflected in an elevation of serum alkaline phosphatase activity. In hypophosphatasia, osteoblasts are present, but alkaline phosphatase activity remains low and calcification is deficient. Neither presence of an inhibitor nor absence of an activator for the enzyme has been found,[3, 6] and so hypophosphatasia is at present best interpreted as an inadequate production of the enzyme.

The function of alkaline phosphatase in tissues other than bone is not clearly defined. No striking differences between enzyme obtained from different organs have been shown, but totally different functions[12] have been attributed to this enzyme when found in other sites, for example, glucose transfer across intestinal and kidney tubular epithelium, phosphate transfer in lactating breast, and protein synthesis in tissues in general. The various postulated functions for alkaline phosphatase have some experimental support. For example, Lundsgaard[10] in 1933 suggested the participation of alkaline phosphatase in renal tubular resorption of glucose. Subsequently histochemical observations[11] localized the enzyme in the

proximal tubules, which is the site of glucose resorption, whereas the glomerulus and distal tubule usually contained none; in addition the toadfish,[11] an aglomerular species with no tubular resorption or excretion of glucose, has no tubular phosphatase activity. It is notable that precipitates of bone salt do not normally occur in these tissues in spite of their high content of phosphatase activity. A multiplicity of tissue-specific functions for what is usually regarded as a single enzyme at first thought appears unlikely, but seems more reasonable when one recalls that alkaline phosphatase can act on a variety of substrates so long as they contain a phosphate monoester bond.

In hypophosphatasia, alkaline phosphatase activity is depressed in all tissues; and one might expect several metabolic defects to appear clinically. Several investigators have looked for such defects in patients with this disease, but thus far the only generally accepted metabolic defect assignable to enzyme deficiency is rickets. Growth retardation, which in some cases appears to exceed that attributable to rachitic deformities, suggests a defect in protein synthesis, but this effect is too nonspecific to be assignable directly to alkaline phosphatase deficiency. Increased renal tubular resorption of phosphate was reported by Schneider and Corcoran,[2] but additional reports of this function in other patients are lacking. Their postulate that this is the primary defect in hypophosphatasia seems unlikely in the light of subsequent data. Neither glycosuria nor impaired gastrointestinal absorption of carbohydrate have been found; thus far no opportunity for measuring the phosphate concentration of milk obtained from a patient with the disease has been reported. The failure to find other metabolic defects in hypophosphatasia may result from the fact that alkaline phosphatase is only deficient and not absent from the tissues; function may therefore be sufficiently well preserved to make detection of a deficiency difficult. The total number of reported observations on physiologic systems other than bone is very small, and one of the best studied cases, that of Sobel and others,[3] had an apparently mild form of the disease with normal growth rate and general health except for rickets. Tests capable of measuring a moderate depression of function often have not been applied; for example, renal alkaline phosphatase activity might be sufficient to prevent a persistent renal glycosuria, but insufficient to maintain the renal threshold for glucose at the normal level. If the multiplicity of functions postulated for alkaline phosphatase actually exists, it seems likely that appropriate studies in hypophosphatasia should ultimately reveal them. Thus far, however, only the role of alkaline phosphatase in calcification of bone proposed over twenty years ago by Robison has been supported.

A further recent observation in hypophosphatasia is of both diagnostic and theoretical interest. One of the difficulties with Robison's theory of calcification has been that the substrate for bone alkaline phosphatase has never been demonstrated. The enzyme can act on a variety of phosphate monoesters, but these are carried in such low concentration in plasma that the enzyme's substrate must come from another source. Some

years ago it was found that glycogen accumulated in cartilage about to undergo calcification and simultaneously the enzyme phosphorylase also appeared.[13] This enzyme converts glycogen to a glucose monophosphate ester, which is a suitable substrate for alkaline phosphatase. The missing substrate for bone phosphatase appeared to have been found, although this was never directly confirmed. Recently, however, an abnormal phosphate monoester has been found[5, 6] in both the urine and plasma of patients with hypophosphatasia. Since substrate may accumulate in the absence of its enzyme, the newly found ester may be either the natural substrate for bone alkaline phosphatase or in some way related to it. The ester is phosphoethanolamine (Fig. 1); it was found during paper partition chromatography of the urinary amino acids in patients with hypophosphatasia and is not present in normal urine.

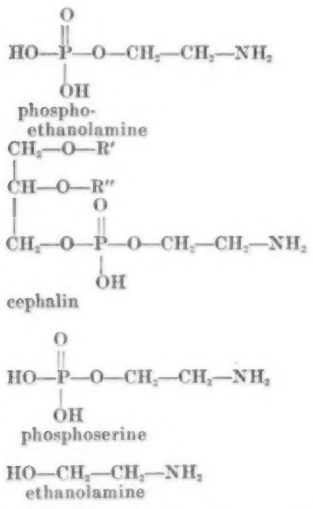

Fig. 1.—Phosphoethanolamine and naturally occurring related compounds.

Its source is unknown. Related naturally occurring compounds are cephalin, which is a cerebroside, phosphoserine, which is formed by phosphorylation of one of the nonessential amino acids, and ethanolamine, which is a precursor of choline. The discovery of phosphoethanolamine in hypophosphatasia patients may clarify the mechanism by which alkaline phosphatase produces a precipitate of bone salt.

SUMMARY

Hypophosphatasia is a newly recognized disease of infants, children, and adults in which diminished alkaline phosphatase activity of tissues and serum is associated with rickets resistant to any known therapy. Sufficient cases have been reported to suggest the disease is not excessively rare. Thus far no abnormality of any physiologic system other than bone has been recognized, although alkaline phosphatase is believed to participate in several unrelated mechanisms, such as transport of glucose across intestinal or renal tubular epithelium, concentration of phosphorus in milk, and protein synthesis. More definitive studies of hypophosphatasia patients may reveal defects in these systems as well as in bone. Recently an abnormal metabolite, phosphoethanolamine, has been found in the plasma and urine of patients with the disease. This observation is of diagnostic significance and in addition may reveal the mechanism by which alkaline phosphatase produces calcification, a point of uncertainty since Robison originally postulated this role for the enzyme over twenty years ago.

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Psychologic Aspects of Pediatrics

THE HOME MANAGEMENT OF CHILDREN WITH SCHIZOPHRENIA

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THE diagnosis of schizophrenia is being made in children with increasing frequency. Increasingly, too, the condition is being recognized in milder forms. Institutional facilities are not available for all the afflicted children nor are they necessary. A report by Silver on the home care of children with schizophrenia is therefore especially welcome. Silver considers institutional care necessary only (1) when the parents are so disturbed that it would be difficult to influence them to an understanding and tolerant attitude; (2) when outlets and satisfactions for the child, as in a school or other group, are unavailable; (3) when the child's behavior is so abnormal that one cannot expect to overcome in a reasonable time the disturbance which he creates in the environment or the danger which may befall himself.

Treatment must take into consideration the extent to which the child's sense of reality is distorted; the depth of his anxiety; his native intelligence and how it is being used; the presence of associated difficulties like reading disability and, on the other hand, the presence of special abilities; the degree to which the child can control or cover up his deviations and the devices he uses for this purpose; the nature of the environment in which he functions; and how the child reacts to his environment.

DRUG THERAPY

Drugs have a definite place in the treatment of schizophrenia. They act by reducing anxiety and, consequently, improving behavior. It is not possible to predict, in any particular child, which drug will be effective, or, for that matter, whether any of them will work. Barbiturates are of little help and sometimes are harmful. Instead of quieting the patient they depress perceptual ability, thereby exaggerating perceptual distortion and increasing anxiety. Unusual reactions to barbiturates are not uncommon in children with schizophrenia. Sodium Amytal frequently causes excitement rather than sedation.

Favorable results have been reported with Benzedrine which produces a feeling of well-being and lessens anxiety. It is given once a day on arising, starting with 5 mg. and increasing up to 20 or 30 mg. if necessary for a therapeutic effect. Unfortunately the action is unpredictable. In children it does not depress the appetite or produce sleep disturbances but it frequently in-

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creases restlessness. It is most useful where the illness manifests itself by sex acts of various sorts. Benzedrine decreases sex interest in adults.

Dilantin is effective in a certain number of overactive impulsive children whose electroencephalograms show high voltage 3 to 4 per second waves. A consistently favorable effect in children with schizophrenia has not been demonstrated.

Benadryl has given gratifying results in children with organic brain disease. In children with schizophrenia, too, it sometimes helps to curb restlessness and to establish a good sleep pattern. The initial dose for children from 3 to 10 years of age is 10 mg. three times a day (one teaspoon of the elixir). This can be safely increased up to three teaspoonfuls three times a day if necessary for a therapeutic effect.

The effects of Serpasil and Thorazine have not been carefully studied in children with schizophrenia. According to Silver, Thorazine is helpful where there are increased motor activity and marked autonomic nervous system lability. Thorazine is said to decrease acetylcholine synthesis and to act on the reticular substance of the brain stem, thus interfering with transmission of impulses to and from the unstable autonomic nervous system. Serpasil does not seem to be as effective as Thorazine in its central nervous system action.

Silver has observed improvement in some children treated with Dramamine.

ELECTROSHOCK THERAPY

The use of electroshock therapy in children with schizophrenia is controversial. It is said to relieve anxiety and thus make management easier. The method has been used by Lauretta Bender in over 500 patients on the Children's Psychiatric Service at Bellevue Hospital during the past ten years. She finds that children tolerate electric shock better than adults and that the procedure does not interfere with intellectual function and development. Though the essential schizophrenic process is not modified the patient's capacity to deal with anxiety and problems secondary to the schizophrenic process is improved. The effect on the ultimate prognosis has not been determined.

Silver finds that the procedure is most beneficial in children with paralyzing anxiety whose symptoms have had a relatively acute onset. It should be given to children only in a residential setting where new patterns of behavior may be formed as old ones are disrupted by the treatment.

PSYCHOTHERAPY

According to Silver most children with schizophrenia will, at some point in the course of their illness, require psychotherapeutic help. Such treatment may consist merely of occasional encouraging talks, or it may mean prolonged, intensive interviews.

The initial task of the therapist is the relief of anxiety. There are many reasons why children with schizophrenia are anxious. At the first meeting, the child is frightened at the new experience, a natural reaction, but here exaggerated and sometimes distorted. The proper handling of this initial reaction is the first step in establishing a favorable relationship with the patient. This situation is met with patience, understanding, and reassurance. The youngster is

told that most children are a little afraid at a first visit to a new doctor, that they come to be helped with this or that specific problem, that many other children have similar problems, that his particular problems can be discussed or something else if he prefers, or that he can play with toys or draw instead.

A deeper source of anxiety is the child's awareness that his feelings, sensations, and experiences are different from those of other children and the fact that he is afraid of expressing them. Schizophrenic children are often concerned about hallucinations, introjected bodies, and abnormal somatic sensations. The disturbed thinking does not come out spontaneously but must be elicited by active though indirect and gentle questioning. The children are relieved to be able to share their experiences and to know that they are understood and that others react as they do.

An important source of anxiety is the child's inability to adequately control destructive, aggressive, and sexual impulses and abnormal body sensations, such as the feeling, experienced by one child, that he was about to explode and that he was flying off into space. He is also afraid that he will hurt himself or others.

Aggressive problems are handled by a calm, accepting attitude on the part of the physician who listens to their verbal expression and their symbolic acting out in play or, not infrequently, in direct action against the therapist. Feelings of guilt should be eased but every effort must be made to keep the child in constant contact with reality. Any interpretation of the mechanisms giving rise to the aggression is made with great caution. Lauretta Bender has pointed out that interpretive analysis may actually be harmful, sometimes releasing forces which the schizophrenic child is unable to control.

A further source of anxiety in the child with schizophrenia is in the psychologic conflicts which are part of everyday living. In the sick child these are magnified and distorted. Such anxiety can be treated in two ways: (1) by reinforcing the defensive mechanisms which the youngster has built up and by helping him to suppress his conflicts; or (2) an attempt may be made to reduce the source of conflict itself.

For many patients Silver recommends helping to strengthen the neurotic defensive mechanisms and making these acceptable to the child and world around him rather than uncovering and interpreting sources of conflict. In most instances the defense mechanisms take the form of compulsions. Silver describes a 9-year-old boy with numerous compulsions such as bedtime, eating, and toilet rituals, speech peculiarities, and so on. The youngster, an only child, dominated the household. It was possible in this case for the patient and psychiatrist to agree to a set of rules whereby the number of rituals was limited to smaller and smaller areas so that life at home became more nearly bearable.

Any attempt to interpret and resolve psychologic conflicts in the child's mind must be done cautiously and gradually and only after a good relationship has been established between doctor and patient. If successful it does reduce anxiety. Many of the youngsters have already been vaguely aware of the sources of their

problems and interpretation therefore means for them confirmation and reassurance.

An important source of anxiety in the schizophrenic child is that which arises from the distortions of mental functioning which are part of the disease itself. An essential disturbance of the schizophrenic process is failure of the patient to appreciate himself as an individual with definite dimensions and oriented in space. He finds difficulty in distinguishing self from the environment. The schizophrenic child experiences sensations of himself or part of himself flying off into space or of himself merging into other individuals or objects. He also feels his body to be distorted—the head large and misshapen, one of his extremities massive, people or machines inside of him. Silver regards this source of anxiety as the most difficult of all to manage. He recommends trying to win the child over to a state of mind in which he regards the therapist as a tolerant, understanding, yet strong individual on whom he can model his own behavior (identification).

The Young Child.—In young children schizophrenia ordinarily manifests itself in severe form. The clinical manifestations such as the lack of interest in persons, the absence or poor development of speech, the difficulty in comprehending speech, and the severe anxiety make treatment extremely difficult.

Gurevitz describes the treatment of a 3½-year-old girl with schizophrenia. At the outset the child was strongly withdrawn, autistic, unable to establish any sort of relationship with people, and greatly retarded in behavior and mental development. She spoke only an occasional word, she was not toilet-trained, her gait was uncoordinated, and she refused all physical contact.

The first effort of the therapist was to establish a relationship with the child. He assumed a passive, tolerant attitude, at the same time implying to the youngster that she was loved, understood, and accepted. Her desires, aggressions, and tantrums were regarded as meaningful to her. Talking to her was used as a technique, even though she did not comprehend the meaning of the words spoken. Gurevitz states that disturbed children react as much to the voice as they do to the content of speech. She was encouraged to draw or the therapist drew for her, using the drawing to make her express herself or as subject matter for conversation.

At first the child whined constantly with what appeared to be lack of any real emotional tension. She wet herself repeatedly and withdrew with revulsion when the therapist tried to touch her. Efforts to attract her with pictures were ineffective. Her attention was finally caught by a cigarette lighter. Other devices used were active games like hide-and-seek, play therapy which was effective in toilet-training her, active encouragement and assistance, repeated expressions of affection and acceptance, acceptance of aggression. After two years of therapy this child was able to make a satisfactory adjustment to her environment.

Bender and Gurevitz have used this approach in five children under the age of 6 years. All the children showed marked improvement.

MANAGEMENT OF THE FAMILY

The effect of having a schizophrenic child in the family is a profound one and differs in many respects from the situation where the child has a serious physical ailment. Silver describes the reaction of the parents as, at first, unwillingness to recognize the seriousness of the illness and a feeling that the peculiarities will be outgrown; then a stage of confusion, a frantic seeking for advice, and further confusion engendered by the conflicting medical opinions offered. A period follows in which the parents feel helpless and unable to comprehend the behavior of their child. His seeming indifference to them makes them feel rejected and they are at a loss as how to cope with the clinging, demanding behavior and with the daily problems of eating, sleeping, dressing, excretion, and social relationships.

At this point parents generally react with the protest, "Why did this happen to me?" Guilt feelings are common, the parents seeking minute derelictions in their behavior to account for the child's unfortunate state. Hostility directed at the child because of his peculiarities of behavior and because of the disturbances which he creates in the home and neighborhood is another common parental reaction. The parents are harassed by gratuitous advice from relatives, the school, friends and neighbors. In addition they often feel isolated and ashamed because of the strange behavior of their children in the community. Other concerns have to do with the child's future development, the financial burdens involved, fear that the psychosis will affect siblings and even themselves.

Once the diagnosis seems definite, most parents can accept a definite statement that the child has schizophrenia, that the nature of the ailment is obscure but that there are many such children and we are learning how to help them. Such a statement tends to give parents confidence in the physician and relieves somewhat their feelings of isolation and uniqueness. The parents need to have some understanding of the nature of the child's illness and of the outlook for the future. In addition, they naturally want advice on how best to handle their difficult situation.

The various concerns of the parents should be discussed. Guilt and hostility feelings are managed, first by encouraging free expression or even expressing these feelings for the parents; and, second, by the reassuring statement that it would be strange if they did not have these feelings under the circumstances.

Special problems in management are discussed as they arise and are handled in a commonsense fashion. Constant encouragement and reassurance that the parents are handling a difficult situation well and are doing a good job is helpful. In some instances the parents are themselves emotionally disturbed or actually psychotic and need psychiatric help. Here the guilt and hostility may mask more serious underlying problems.

Group therapy for the parents of children with schizophrenia is particularly appropriate in view of the common problems of these children as they relate to both the home and the community. On the Children's

Psychiatric Service, Bellevue Hospital, where this therapeutic approach was initiated, 1½- to 2-hour sessions are held weekly. The groups consist of eight to twelve persons. It is advantageous for both parents to attend. Discussion is spontaneous, the therapist remaining in the background and providing interpretations from time to time as indicated. It has been found that the groups quickly develop a sense of unity.

Initially an attitude of confusion and bewilderment about the behavior of their sick children is shared by the group. The parents describe their children as total enigmas. Later, feelings of guilt, hostility, social pressure, isolation, and hopelessness come out.

Group therapy is helpful in many ways. Resistance to cooperation in therapy for the child is overcome. An opportunity is afforded to give support in the handling of specific problems and advice for general management. At Bellevue Hospital the most faithful group of participants was found to be parents with deeply rooted personality problems of their own. In them the results were most satisfactory. Interparental relationships were improved, the tendency to blame the conjugal partner for the child's unfortunate state, and in this way to relieve oneself of guilt in part at least, was dissipated as insight grew.

Problems of social pressure, social isolation, and helplessness are particularly well handled in groups. The parents find strength in being members of a group with a common problem. In New York City some of them have combined to mobilize community resources to help schizophrenic children. In this way they not only have the satisfaction of making a useful social contribution, they feel, as well, that they are helping toward the discovery of methods to help their own as well as other children and, perhaps, in learning how the condition may be prevented.

It is the opinion of Peck, Rabinovich, and Cramer that the majority of parents are helped by getting better insight into the child's abnormal behavior and by a dimunition of tensions in the home, in some instances to a remarkable degree. This has made it possible for some children to remain at home who would otherwise have to go into institutions.

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Pediatric Profiles

A. Graeme Mitchell

(1889-1941)

"Dr. Pottlesmith"

GRAEME MITCHELL was born in Salem, Massachusetts, the center of American witchcraft, grew up in Philadelphia, the city of brotherly love, and spent his years of maturity in Longfellow's "Queen City of the West," Cincinnati. Perhaps his birthplace may have contributed to his vivid imagination and his restless nature—perhaps to his love of an anecdote, although his ability to turn a "story" might well belong as much to his Irish ancestry, being nurtured a bit by a short stay during his youth on the green shores of Ireland. Perhaps it was Philadelphia's implied "I am my brother's keeper" which contributed to his great need to be liked, admired, respected, and, on the other hand, to his ability to give of himself to others. Perhaps it was the cultural center of the boisterous "West" which helped to bring out his artistic nature, but just as well one might suggest that it was the aggressive "Midwest" which stimulated and developed his capacity to build and to administer.

Such deductions are perhaps no better or no worse than the numerous others which have been brought forth to explain the many-sided person Graeme Mitchell came to be. Of those who arrive at pre-eminence and prominence, few can hope to escape the analytic dissections aimed at explaining the "why" and the "how" of greatness. Many have attempted to put their fingers on what made him tick. Obviously there have been varied explanations. But whatever it was that carried him to the top, it was generally agreed that he rated what he wanted and needed most—friendship, respect, and admiration. Physician, scholar, teacher, investigator in the broad sense, builder, administrator—all of these he was, and in all he was adequate.

Few persons in academic pediatrics have been as widely known on a personal basis, or better liked by the large group of practicing pediatricians in this country than was Graeme Mitchell. He was a natural leader and in large

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It is not possible to give credit to all of Dr. Mitchell's associates and friends who have assisted in the preparation of this Profile, but Mrs. Mitchell, Paddy Rudd (Mrs. William Howes), and Dr. Josef Warkany do deserve special recognition.

groups and in small ones he tended to stand out, without attempting to monopolize the scene. There was the essential knack of being impersonal and of diverting embarrassing situations. His love of storytelling sessions was well known, and his ability as a raconteur became almost legendary.

Mitchell received his doctorate of medicine at the young age of twenty-one, having graduated from the University of Pennsylvania in 1910. His story of his admission to the University is evidence of his determination and capacity for work. His application for admission to the University following graduation from Central High School of Philadelphia was rejected because of lack of credits, particularly in Latin and chemistry. He asked permission to be admitted to the fall term on the basis of examinations in these two subjects. He studied each during the summer months and apparently much to the surprise of the school officials passed the examinations. This capacity for work was reflected in his activities of later life. One of his characteristics was the effective use of "extra" five- and ten-minute periods throughout the day. A significant part of the work on his book was accomplished in this way.

Upon his return from World War I in which he saw active duty in the French amphitheater, he became increasingly aware that his medical interests were in the academic field rather than in private practice. His reception in Cincinnati was a warm one by medical students, faculty, and practicing physicians alike. To the students he brought a bright, stimulating approach and soon gained for pediatrics the popularity which it continued to enjoy under his direction. To the residents, Mitchell was reflected at his best in ward rounds and in his conferences, regular ones and informal ones in his private office. Ward rounds were never dull. By his own evaluation, he had to work at being patient with the evolution of the differential diagnosis from the history, physical examination, and laboratory data. Although he usually grasped the significant points quickly, he would permit the resident to develop the case in his own way, interjecting remarks only to establish or cement specific points. But on occasion he could not resist the fun of making a snap diagnosis with only limited information. He had an uncanny knack of "guessing" correctly. As might be surmised, this trait tended to stimulate a desire on the part of the residents to stump him. There are many stories of such efforts. On one occasion when a girl with a dextrocardia and transposition of the abdominal viscera was to be presented at rounds it was decided to make no comment relative to the anomaly. He apparently suspected that a trap had been laid, but said nothing. In establishing friendly relations with the child, he lightly laid his hand on her chest, perchance on the right side, and as he did a sparkle came to his eyes. "Such a nice and pleasant young lady and to think she doesn't have her heart in the right place." The resident who had conceived the plot could do no better than, "The luck of the Irish, you can't beat it."

In appearance as well as in speech he was jaunty, bright, actually almost immaculate. About the hospital, by contrast with some others his always clean and always neatly pressed and starched white coat stood out. At meetings, so frequently in bow tie, pipe in mouth, and clothes in good taste, he

was an attractive figure as well as a popular one. His bald forehead, bright, sparkling blue eyes, finely chiseled nose, and ready smile became his identification which was often reflected in "There's Graeme," with the implied thought that the meeting would now be a success.

Mitchell's contributions to pediatric meetings were many, but perhaps he was best known as a moderator of group or panel discussions. He had uncanny abilities to make the ideas of others flow more freely, to coordinate the presentations of the various participants, and to keep to the subject and thus avoid confusing deviations. And perhaps as important he could bring the meeting to a close within the prescribed time and with the maintained interest of the audience. In the minds of many he is still the leader of panel discussions against whom the abilities of others are measured.

It is interesting that two of the widely and favorably known figures in pediatric circles during the period of its rapid growth have been storytellers of the first order. Yet when business was the order of the moment each could be completely serious. One, of course, was Mitchell and the other his good friend, Joe Quilligan. In Cincinnati we came to look forward to Joe's visits, knowing that a "session" was inevitable. Some of these sessions, especially several at times of state or national meetings, have become fairly well established as a part of anecdotal pediatric history.

Quilligan and Mitchell

At the Academy of Pediatrics meeting in Kansas City in 1936, Bilderback, Wylie, and Mitchell set the stage for a session which is also firmly established in pediatric history. A few of us had assembled for dinner in one of the smaller dining rooms of the President Hotel. As might have been expected, there were Heidelberg songs, Apache dances, and, of course, stories. There was an air of contagiousness. As the crowd grew, one of the staff of

the hotel's management wishing to contribute his share had a piano and a female pianist brought into the room. They were scarcely necessary, nor welcome. Bilderback became spokesman and requested that both be removed and that the "woman" be returned to the street where she belonged. But the gentleman in Bill was too secure, the words were not more than uttered when he was at her side apologizing—she knew not for what. But she was adequate to the situation and in every respect understanding. She withdrew and the party continued.

As a toastmaster, Mitchell was frequently in demand, and the banquets at the annual meeting of the Academy in Cincinnati in the thirties, the ABC (Abt, Brennemann, Cooley) celebration in Chicago, and the Mayo gathering in Rochester will be long remembered as evidences of his deftness as a master of ceremonies. It is one of the current classics to hear Cliff Grulee recount Mitchell's introduction of Fishbein at the Mayo banquet.

But Mitchell was not always the lighthearted one. In fact he was not only deadly serious about his various responsibilities but he was by nature a worrier. He had to work at the business of being buoyant. He worried about his department in the medical school, the Children's Hospital, the Research Foundation, his family, his health, and even his story-telling. For the last he kept a "book," and the various types were classified and catalogued. Rarely did he attend a public gathering where he might perchance be called upon without making beforehand appropriate notes on a card which he would palm during his "impromptu" remarks.

Mitchell had to have hobbies. They were essential to his dynamic, restless way of life. But he could not play at them nor take them lightly; they had to be worked at. Collecting-wise he assembled a respectable (in size—not always in subject matter) group of medical caricatures. But his heart was in his painting (water colors), etching, and dry points. These he did sufficiently well to "justify framing and giving them as gifts to his friends" (a bit more of this later) and hanging them *permanently* in his own study if not in the family living room (cf. his remarks in "Pottlesmith on the Amateur Art Critic"). Actually his hobbies did not provide him the relaxation he needed so much, but at least they did provide diversion. That they were directed to artistic channels was natural. Mitchell was innately an artist. His ability to get perspective in his paintings and his etchings was reflected in his perspective of situations, his analysis of people and his capacity to handle problems on as nearly a non-traumatic, impersonal basis as possible.

Being an artist, Mitchell was extremely sensitive. Although this character served him in good stead in helping others, it was costly for him in that he was easily hurt. Remarks, which would have been unnoticed or overlooked by a less reactive person, would leave a permanent scar on him. Perhaps this trait is reflected in degree by the saying which he had imprinted at the foot of his personal stationery: "Life is not complicated if you reduce it to basic facts and motives. It is the people who live the life who make it complicated." On one occasion after a painful episode with one of the junior house staff, this undisciplined youth secured a sheet of this stationery, encircled the saying and identified it by an arrow with his scribbled re-

mark, "Why not practice your preachments?" I am confident that this then callow youth is one of Mitchell's strongest admirers and looks back with appreciation for lessons learned. But Mitchell brooded over the incident for days.

Like many another, Mitchell found an outlet through an alter ego to whom he attached the pseudonym Dr. Pottlesmith. Pottlesmith was aptly described by Paddy Rudd (secretary to both Dr. Mitchell and Dr. Pottle-

"The Market"
Dry point etching by Mitchell

smith) as "an erudite, pompous, philosophic, and professional gentleman given to verbosity but full of wit and wisdom." On occasion, even in letters, Mitchell gave way to Pottlesmith to hand on some philosophic tidbit or a pointed truth deemed helpful to the recipient. Likewise in speaking from the platform he found Pottlesmith a ready and useful source of reference. In his "Pottlesmith on the Amateur Art Critic"* one sees clearly not only that his painting and etching provided an outlet for his restless and dynamic selves but also how even in his hobbies his sensitivities were close to the surface. It was in this manuscript that I found myself revealed as one of the unwitting contributors to his discomfiture. ". . . Pottlesmith has no delusions about his . . . painting and etching. . . He aspired only to reach that advanced state where he could give his productions away without such added inducements as frames. It had hurt . . . when he recognized frames he had bestowed with his own handiwork later enclosing the artistic effort of another." The "Chief" had come to our house on a Sunday morning for some paper work. Sitting in my study he pointed to a

*Mitchell, A. Graeme: The Print Collector's Quarterly 28: 322, 1941.

picture on the wall and asked, "What is that painting?" My response, "Oh, just one of Jane's masterpieces." Jane must have been about eight years of age at that time. Several days later, when her mother, in my presence, remarked "Why, Jane, you shouldn't have covered Dr. Mitchell's painting," did the complete significance of the initial query dawn on me.

Dr. Pottlesmith could express what Graeme Mitchell was unable to say, either because of a dislike of sounding pompous or because of lack of opportunity. He was an armchair philosopher, slightly given to verbosity (and accused by his creator of pomposity), expressing that part of Dr. Mitchell's personality which had no outlet during his busy days. It was Dr. Pottlesmith who made the large collection of medical caricatures (Rowlandson, Daumier, Hogarth and many others) which decorated the walls of his inner office; it was Graeme Mitchell who made them the subject of an illustrated lecture which he gave generously. It was Dr. Pottlesmith who led Graeme Mitchell to take up etching and watercolor painting and Pottlesmith who made fun of the amateur art critics who looked over Mitchell's shoulder. It was Pottlesmith who wrote philosophic and humorous essays; it was Graeme Mitchell who wrote textbooks. There had to be an outlet for expression by the whole of this very human person, and it was only to be expected that he should wish to deserve recognition as a writer if not as an artist. One of the happiest Pottlesmithian events was the acceptance for publication in *The Print Collector's Quarterly* of Graeme Mitchell's article, illustrated with three of his etchings, entitled "Pottlesmith on the Amateur Art Critic," and bearing as a frontispiece the caricature by Wheelan of Dr. Mitchell in the role of Dr. Pottlesmith. Unfortunately it did not appear in print until October, 1941, five months after his death.

It was in his family that Mitchell found his greatest satisfactions. His way of life and his many public responsibilities did not permit him to be a homebody in the generally accepted sense. Even when he was at home much of his time had to be diverted to his work, especially to The Book. But his love and devotion for Adele (Wentz) and the twins, Kathryn and Marie, were unquestioned. Without their willingness to fit their activities to the irregularities of his busy life he could not have accomplished the many things which made him the leader he was in the pediatric field. One of his colleagues on occasion questioned if Mitchell really appreciated the extent to which Mrs. Mitchell adjusted the pattern of their home life to fit his needs and even in a sense guided and directed him. There was no question of her devotion to him or of her willingness to personally do all that she could to aid and abet him in every way. I am confident that he knew and was in every way appreciative. In his "Pottlesmith on the Amateur Art Critic": "It happens that Mrs. Pottlesmith is adamant about a few things, although in most respects she is skillfully acquiescent to Dr. Pottlesmith's peculiarities."

His wonderment concerning Kathryn and Marie, the twins, never ceased; they were something heaven sent—and his pride in their charm and loveliness as they approached maturity never lacked evidence. He had a variety of stories to attest to his part in their upbringing, but none perhaps that he liked more than *his* account of his

early morning "milk route" in Philadelphia when he collected each day a supply of breast milk from a variety of sources during the first few months of their lives. It was his boast (according to Adele's good friend Mrs. John Porter [Frances] Scott) that at this stage he kept eight women. The "harem" included Mrs. Mitchell, her nurse, the twins, and the wet nurses. His personal satisfaction in being chosen to give the commencement address at the graduation of the twins from Hillsdale School is evident in the address which he wrote just prior to his death and which was read posthumously.

When Mitchell arrived in Cincinnati in 1924 to assume the professorship of pediatries in the College of Medicine, plans for moving the Children's Hospital and erection of a new structure in the medical school group of buildings were under way. But he was on the ground in time to play a major part in planning the new building and to him must be given much of the credit for the development of the hospital and the Department of Pediatries into one of the leading pediatric units of the world. During his tenure, the new Children's Hospital, the Research Foundation with its separate building, and the Children's Convalescent Home all came into being; in all he had a leading part. He was also active in city and school health functions, serving on the City Board of Health. He encouraged and made it possible for Bob Lyon to give a substantial part of his time to public health activities. The current effectiveness of the Babies Milk Fund Stations (child health conferences and home pediatric services) distributed throughout the city, which had been started by Rachford, must be credited largely to Lyon and indirectly to "The Chief." The assumption that Mitchell's impact on and his contributions to the growth and development of child health facilities in the Cincinnati area stand out clearly beyond those of any other would not be challenged by many.

Nationally Mitchell was very much a part of the pediatric scene. He was active in the American Academy of Pediatries from its inception, and served on the council of the American Pediatric Society. In each of the White House Conferences on Children held during his medical lifetime (1929-1940) he was one of the leading figures. Although he served as medical consultant to the National Foundation for Infantile Paralysis for a few years, he sensed and pointed out the inherent dangers of Funds for Diseases and the need for highly objective medical guidance of them. He would be greatly concerned over the recent rapid increase in the number of such funds and the lack of adequate control of them.

The Book (Griffith-Mitchell: *Textbook of Pediatrics*) never provided him the satisfaction he desired and deserved. He never became its master, but instead he was its slave, and in certain respects an unwilling one. Griffith and he never achieved an adequate teammate status; nor did they appear to have much in common on a personal basis. The book as originally prepared by Griffith was printed in two volumes and had a definite encyclopedic quality, containing an amazing amount of documented information. The two-volume text went through two editions. The book had a good acceptance in this country and abroad among practicing physicians, but it was not widely used by medical students. This bothered Mitchell and

the publisher. With stimulation and support from the latter, it was decided to condense the book to a single volume and to shift the emphasis more toward the essay type of text. This was a painful procedure. No one probably really knows what this job took out of Mitchell nor the struggles he had with Griffith over big and little points alike. But Mitchell felt and showed the strain.

In the next two editions (1937 and 1940) the effort to make the book more acceptable to students continued. Griffith never completely acquiesced and the disagreements seemed to come over increasingly smaller items. Mitchell so much wanted to have one edition solely his own, even to bearing only his name. It was one of the few rewards which he was denied in his short but brilliant life. Even in the last edition of the Griffith-Mitchell series (third of the single-volume series) there were problems of a considerable order. It had become increasingly clear that one person could no longer be expected to be critically adequate for all phases of pediatric medicine. Instead of asking others to write specific sections of the book, and he in turn fit each one to his measure of a textbook, he reversed the process. He assembled and wrote the material and then sent each chapter to an authority in the respective subject for criticism. This experiment provided many additional headaches, and although the system might have been made to work in subsequent editions, for this one it only added to the strain.

The American Pediatric Society had met in Hot Springs, Virginia, in the spring of 1941. On a May evening in Philadelphia I had a telephone call from Cincinnati. It was "The Chief" in his lightest vein and best form. What had I done to merit membership in the American Pediatric Society? Certainly he did not know. Had I finally learned about pipe tobacco and gone over to a good variety (an old feud)? And so went the conversation. Several days later there was a call from Mrs. Mitchell. "Graeme wants to see you." I answered lightly, "Good, when is he coming?" The answer, I shall never forget. "But, Bill, didn't he tell you, he's sick!—He is dying." He had passed on when I arrived in Cincinnati. His telephone call to me was from an oxygen tent and against "orders."

Mitchell's death in the prime of his life came as a great shock to the pediatric world. Perhaps the loss of no one had seemed more acute owing to its untimeliness. But next to that of his family the loss was greatest for the group which meant so much to him, his residents, ex-residents, and hospital family.

". . . Most important there were incentive . . . and an esprit de corps in the group he commanded.

"There never was any question of a fair deal for the individual. I can recall many a time when there were rough spots—but almost invariably they were smoothed out before the day was over. He was restless—sometimes impetuous—but these qualities were buffered by a great adequacy in judgment, which at times seemed almost more intuitive than considered. But his mind worked so much more rapidly than that of the average individual that one was scarcely aware of the balancing of the two sides of a question. He was an artist—and had the intuitiveness of the creative mind which provided a quick understanding of a situation of the moment. More than once I have heard him say, 'It seems that even after I weigh all the

possibilities in a given situation, I come back to my first hunch.' It was this quality coupled with his love of people which so endeared him to those with whom he came in intimate contact—and which was responsible for the great love and devotion explicit in terms related to his resident staff. Though he was affectionately known as 'The Chief'—and we termed ourselves the slaves and ex-slaves, he termed himself 'Poppa' and us, his 'illegitimate children.' An outstanding evidence of the devotion to Doctor Mitchell and to Children's came at the time of the 'Ex-Slaves' Reunion' in the mid-thirties. Ex-residents came literally from all parts of the country —and in the truest sense it was a family reunion. Perhaps no other evidence of loyalty and devotion gave Doctor Mitchell more genuine satisfaction.''*

*From "A Memorial to Doctor A. Graeme Mitchell" by W. E. Nelson, at the presentation of his portrait to the Children's Hospital, Cincinnati, Ohio, September 27, 1951.

And so! What is the pattern of the man whose influence is still felt in the pediatric world as well as out of it and to whom so many feel indebted? Warm, lovable, kindly—humorous, witty, entertaining—dynamic, administrative—and counselor—all these he was and all were factors in the composition of the man Graeme Mitchell came to be. But these attributes do not delineate the astute clinician (they do explain the kindly physician), the able teacher, the medical writer, the developer and builder of a great pediatric department, nor the leader in national medical affairs. For these things Mitchell has earned a place in pediatric history. But it is likely that if a choice were required he would choose to be retained in the hearts of those he termed "his own"—his family, his friends, and his "hospital family."

—*Waldo E. Nelson.*

Comments on Current Literature

SEQUELAE IN ARTHROPOD-BORNE VIRUS ENCEPHALITIS

DURING the summer of 1952, an epidemic of acute encephalitis occurred in California, the clinical diagnosis of encephalitis being made in 813 cases. Of these cases, 375 were confirmed by appropriate laboratory studies and the infection classified as equine encephalomyelitis, Western type; 45 cases were classified similarly as encephalitis of the St. Louis type. This unusual clinical experience, enhanced by extensive laboratory studies, prompted the California investigators to undertake a follow-up study of these patients in thirteen clinic centers, well distributed in the Central Valley area.

A preliminary report of this clinical follow-up study, covering a period of eighteen months, appears in the April, 1955, issue of *Neurology*.[1] Included in the follow-up study, in addition to 334 patients from the 1952 epidemic, were 113 patients ill with encephalitis in 1950, 1951, or 1953, bringing the total number of patients followed to 447. The basic criterion for listing postencephalitic sequelae was considered as "any neurologic or psychiatric abnormality which seems to be attributable to encephalitis."[1] These manifestations ranged from mild emotional disturbances to severe neurologic damage.

The large 1952 epidemic was investigated carefully, and several aspects of the clinical manifestations seem of particular interest. Age range, apparently, was a pertinent factor in the various types of encephalitis; the general total included patients ranging in age from a few days to over 80 years. Concerning the St. Louis type, it was of interest that only three cases of St. Louis encephalitis in infants have been proved in the state of California during the past eight years; in contrast, 20 to 30 per cent of the cases of Western equine encephalomyelitis occurred in patients under one year of age. In the epidemic described, convulsions were a problem in young children, especially in infants under one year of age, occurring in 75 to 80 per cent of these infants. Convulsions were less characteristic as a manifestation in older children: 1 to 4 years of age, 30 to 35 per cent; 5 to 14 years, less than 10 per cent. The occurrence of convulsions has significance, in that infants or young children who had convulsions during the acute phase of the illness showed a higher percentage of the severe types of sequelae. In adults, the most consistent clinical observation, apart from the usual meningeal and encephalitic signs, was the presence in almost every case of severe occipital headache. Stupor and coma occurred in 35 to 40 per cent of the adults, and disorientation and mental confusion were common findings. Convulsions were rare in the adult

group. The authors emphasize that "The most dramatic over-all clinical observation in all age-groups" was "the sudden remission of symptoms and signs."[1]

In the epidemic of 1952, there were 58 fatal cases among the 813 diagnosed clinically as encephalitis, or a mortality of 7.1 per cent. However, of the 420 cases confirmed immunologically by laboratory studies, a case fatality of only 2.4 per cent was observed. In the clinic centers the patients were seen as often as possible; this was especially true of the 1952 epidemic, two-thirds of the patients being seen in the follow-up clinic two or more times. A summary of data obtained on these visits for the 447 patients with encephalitis (from outbreaks in 1950, 1951, 1952, and 1953) revealed that 142 patients, or 32 per cent, had sequelae at the time of examination. It was a consistent observation that infants under one year of age seem particularly vulnerable to the virus of Western equine encephalomyelitis. Of 98 infants in this category, 53 had sequelae which were classified as of three main types: convulsions, behavior retardation, and upper motor neuron signs. Infants who had encephalitis at the age of 3 months, or under, were severely affected, sequelae resulting in well over half of those ill during the first three months of life. A sharp fall in the incidence of sequelae (to about one-third) in infants older than 3 months at the time of illness led the authors to conclude that if an infant does not develop encephalitis until after he has reached this age, his chances of recovering without severe sequelae are good. They emphasize likewise the fact that many of these children tended to show improvement during the course of the ensuing two to three years. However, two of these patients who had encephalitis during infancy are now institutionalized, and four others are considered completely helpless. Of those patients who had encephalitis between the ages of 1 and 4 years, 19 of 54, or 35 per cent, had sequelae, the greatest incidence of such aftereffects in this instance being in patients who were ill with encephalitis around the age of one year. In the group having encephalitis at ages 5 to 11, the subsequent difficulties were largely subjective in nature. Only a few of the older patients showed residuals which give rise to abnormal neurological signs; 20 of these 78 patients had neurological or psychiatric complaints, five showing such neurological signs as hemiparesis and tremor. In the adult group a prolonged recovery period was characteristic, symptoms of headache, easy fatigability, etc., disappearing gradually. Not more than 5 per cent of adults showed sequelae of any practical significance, and none of these patients developed parkinsonism. Electroencephalographic examination of 140 patients failed to reveal any trends significantly abnormal.

In this remarkable study the authors demonstrate the value of a well-planned and well-executed clinical investigation which is supported by careful laboratory tabulations. As the study is extended, further information should be available concerning the ultimate outcome of patients

who have suffered from infection with viruses of the so-called summer encephalitides. From the epidemiologic point of view it is apparent that mosquito control should be carried out consistently, and that the very young infant who seems especially vulnerable to the arthropod-borne viruses (notably Western equine) should have adequate protection at all times.

RUSSELL J. BLATTNER

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News and Notes

The Preliminary Program for the **VIII International Congress** which will be held at Copenhagen, July 22 to 27, 1956, has been issued. Ten Plenary Sessions will be held forenoons:

Monday, July 23:	I. Prenatal Injuries and Malformations
	II. Chemical Agents
Tuesday, July 24:	I. Pathology of the Newborn: Anoxia
	II. Surgery
Wednesday, July 25:	I. Child Psychiatry
	II. Neurology
Thursday, July 26:	I. Infections
	II. Allergy
Friday, July 27:	I. Problems in Tropical Pediatries
	II. Tuberculosis

On all but Wednesday afternoon the meetings will be divided into sections for proffered papers.

Two round-table conferences will be held on each of the four afternoons for the following subjects: (1) Auricular septal defect; (2) Epilepsy; (3) Leukemia; (4) Hemophilia; (5) Amino acid metabolism; (6) Nephrosis; (7) Water and electrolyte metabolism in dehydration; (8) The adrenogenital syndrome.

Scientific and technical exhibits will be held at buildings close to the meetings in the University buildings. Films will also be shown in the exhibit buildings. The fee for enrollment, full members must be members of a National Pediatric Society, is 250 kroner (Danish) up to Jan. 1, 1956, and 350 kroner from Jan. 1 to May 1, 1956. No enrollment will be accepted after May 1, 1956. The fee includes Congress publications.

The opening ceremonies will be held Sunday afternoon, July 21, and Wednesday afternoon has been set aside for an excursion given by the organizing committee. Prof. P. Plumb is president of the organizing committee.

The **Institutes** for physicians and nurses **in the Care of Premature Infants** at The New York Hospital–Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, are currently in their seventh year of operation. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers, and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses of four weeks' duration. Participants pay no tuition fee and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the 1955-1956 year are definitely scheduled to start on the following dates: Sept. 26, 1955; Nov. 21, 1955; Jan. 30, 1956. In addition, if the number of applicants is sufficient to warrant it, fourth and fifth Institutes will be scheduled beginning: April 2, 1956, and May 21, 1956. Early application for these Institutes is essential since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 East 68th St., New York 21, N. Y.

The **American Psychosomatic Society** will hold its thirteenth annual meeting at the Sheraton Plaza Hotel in Boston on Saturday and Sunday, March 24 and 25, 1956.

A gift of $500,000 has been made by the H. J. Heinz Company Foundation, the Howard Heinz Endowment, and H. J. Heinz II to Children's Hospital of Pittsburgh for the establishment of research chemical laboratories which will be known as the Heinz Laboratory of Children's Hospital. In announcing this gift Mr. Heinz said, "The work of Children's Hospital in increasing its outpatient services, its educational program and its pediatrics research deserves the admiration and support of every Pittsburgh citizen. The importance of laboratory work in our own business made it seem that the creation of a thoroughly equipped laboratory would be the most appropriate type of gift we could provide for Children's Hospital to assist it in attaining the immense objectives it has set for itself." The Heinz Laboratory is to be a part of a new building now being planned.

Applications for the residency from July 1, 1956, to June 30, 1957, in Pediatric Oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to Nov. 1, 1955. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually, plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th St., New York 21, N. Y.

Books

Adoption . . . and After. Louise Raymond, New York, 1955, Harper & Brothers, 238 pages. Price $3.00.

According to estimates of the Children's Bureau, some 70 to 75 thousand children are being adopted in the United States each year, of which about one-half are privately adopted or placed in adoptive homes by state agencies. It is a problem that involves social agencies, the "gray market," and as has been strikingly publicized recently by Senator Kefauver, the "black market." The author, a literary editor, and the mother of an adopted child, has written an excellent book on the problems of adoption which can well be recommended to couples who have in mind the adoption of a child. Two of the chapters stand out of particular practical value. The chapter on "What you should know about yourselves" goes into the reasons why experienced social workers in agencies involved in the field of adoption show preference for certain couples and turn down others. A difficult thing for some people to understand. Perhaps the most important chapter is the one on "Telling your child he is adopted." The book closes with a list of "Adoption Agencies" by states. One chief criticism of the book is not the advice or point of the discussion, but rather its verbosity. While the unusually well-educated couple will probably get a lot out of the book, the discussions are too involved for the average American couple who have not gone beyond grade school. A careful pruning of unnecessary case illustrations and discussions, and of reference to writers and to reports in the field of adoption would have made it a more readable book.

Report of the Committee on the Control of Infectious Diseases of the American Academy of Pediatrics, 1955 edition. American Academy of Pediatrics, Evanston, Ill., 83 pages. Price $1.00.

This excellent report with its frequent revisions and gradual enlargement in scope has become an accepted authoritative manual on immunization procedures. The present revision shows extensive thought and work on the part of the Committee. The text went to press advising the use of the Salk vaccine based on its 1954 use. An insert page reports a meeting of the Committee on June 15 at which an action was taken recommending that injections be discontinued for the present, in view of the difficulties which have arisen in the manufacturing, testing, and usage of the vaccine. Nonmembers of the Academy may obtain this useful report from the Academy headquarters in Evanston.

Prolonged and Perplexing Fevers. Chester S. Keefer, M.D., and Samuel E. Leard, M.D., Boston, 1955, Little, Brown & Co., 248 pages. Price $5.50.

While this book deals chiefly with perplexing fevers in the adult, there is considerable material in the book of interest to the pediatrician. The discussion of variations in normal body temperature in the first part of the book is adequate and interesting. A section on the infectious fevers follows the introductory chapter, and the final section takes up the noninfectious cause of fever such as tumors and the collagen diseases. The authors stress that the use of antibiotics and other agents as cortisone have considerably altered the usual clinical picture of obscure or prolonged fever.

Practical Endocrinology. Lewis M. Hurxthal, M.D., New York, 1955, McGraw-Hill Book Co., 318 pages. Price $7.00.

A volume in a series of handbooks for the general practitioner written by Dr. Hurxthal of the Lahey Clinic and his associates.

The Management of Mental Deficiency in Children. I. Newton Kugelmass, M.D., New York, 1954, Grune & Stratton, 312 pages. Price $6.75.

Editor's Column

CAVEAT EMPTOR

WITH over 37 million babies born in the United States in the ten-year period ending mid-1955, and an expectancy of 42 million in the next ten years, it is not difficult to see why business has been booming for companies dealing in products for use in infancy and in early childhood. It accounts for the tremendous expansion in advertising which has taken place in this field, and the desire of business firms to seek advertising media which tend to expand the sale of their products. Media which reach physicians who care for children are much sought after.

It has been the policy of THE JOURNAL OF PEDIATRICS to restrict its advertising to articles used in therapy. Since preventive pediatrics is a most important phase of "therapy," it accepts the advertising of products important to normal growth and development. The final decision as to the admission of a product, or of the advertising copy submitted, rests with the Editorial Board and not with the publisher, although the advertising section is a function of the publisher. In recent years there has been little trouble, as most companies have come to understand the principles and details that make a product or copy acceptable or unacceptable. When difficulties do occur, we have come to feel they are not so much the fault of the companies themselves, as that of some uninhibited copywriter in the advertising agency who fails to distinguish between copy acceptable to a lay publication and to a medical journal. At times the decision to accept or to reject is difficult to reach.

A knotty problem came up recently when space was sought to advertise a health insurance plan. The request was rejected by the advertising manager of the JOURNAL on the basis that it had no relation to therapy. An appeal was made to the Editorial Board on the basis that the plan was for health insurance for infants in the first year of life, and of advantage to the pediatrician. In discussing the plan with some physicians in practice, the Editor found that the questions raised were of so much interest that it is felt our readers would be interested in the problem and our decision.

Briefly, the plan calls for payment up to $250 for medical service for illness developing in the first year of life over and above a stipulated sum agreed upon between the physician and parents for normal supervision such as feeding instructions, immunizations, etc., during the first year of life. The plan is fostered by one company and the insurance policy issued by another. Both are located in the same city and obviously there is a close working association. The physician is to present

the plan to the parents by means of a brochure. It is to be offered only for babies who are normal and healthy, and thus presumably for infants who will not develop serious illness calling for much additional medical service in the first year of life over the usual normal care and supervision. The appeal made to the physician is that it will guarantee him payment for his medical services should such need arise in the infant's first year. As an additional inducement, the plan is urged as a method of combating the old red herring of medical socialization.

In analyzing and considering the plan, several points stand out.

1. It *forces* the pediatrician to institute supervisory care, immunizations, etc., for the first year of life on a stated fixed-fee basis. While this method has been successfully used by some pediatricians for many years, and we understand is in quite common use in some communities, there are many pediatricians, probably the vast majority, who do not use the fixed-fee plan for normal care of the infant.

2. *The doctor becomes an insurance salesman for this specific company,* despite statements to the contrary.

The physician is furnished with a "kit" (which for "legal" reasons he must request) of brochures containing application and claim forms. He gives the brochure, which contains an application form partially filled out by the physician, to the parents. After the application form is signed by the parents, it is returned to the physician who signs it and mails it to the insurance company. In other words, the contact with the parents and the handling of the application are by the physician. In case of a claim arising, the physician is the intermediary between the parents and the company.

3. According to available information, which we believe to be correct, the insurance company issuing the policy is a recently formed company (1952) with a small capital as insurance companies go. We have been told it is licensed to transact business only in the state where it is located. Such a company, we are informed, cannot do business through agents in another state unless it is also licensed in the particular state. There are many similar companies who solicit business for health and accident insurance policies by mail. We have no opinion as to the reliability of this particular insurance company.

Granted that complete medical care of the infant in the first year of life is a laudable goal, and that health insurance of some sort is desirable, in this particular plan the exploitation of the personal relationship existing between the physician and the parents of the baby for the benefit of a profit-making insurance company raises serious ethical implications. Aside from this, should any disagreement occur between the policyholder and the insurance company, as so frequently happens in the case of health and accident insurance policy claims, the blame, rightly or wrongly, will be placed on the physician by the parent. He will feel the physician induced him to take out the policy.

On the basis of this analysis of the plan, advertising space in the JOURNAL was denied.

THE REHABILITATION OF CHILDREN

IN A report in this issue on page 461, Kanof relates the experience of a unit established in Brooklyn for the rehabilitation of handicapped children. While Kanof stresses that the supervisory function be delegated to the pediatrician, what seems to be essential is for the pediatrician to be equipped by training and interest to supervise and plan the general problem of the care of a handicapped child. While in most communities similar units do not exist, and probably are not even feasible, nevertheless the pediatrician by calling on the various facilities available in his community or locality can accomplish much toward the rehabilitation of the particular child.

All too frequently with a handicapped child the stress is placed on the correction of the primary handicap, without giving sufficient attention to the concomitant handicaps which result from the primary handicap. Thus a child with a motor defect may never be given the opportunity to develop his mental potentialities to the fullest extent, or a speech difficulty may interfere seriously with his social adjustment. A child who is unhappy or frustrated as a result of some handicap may develop profound psychologic changes.

It is the responsibility of the pediatrician who has a handicapped child under his care to consider the total picture and problem. He cannot simply consider his responsibility is over by referring the child to the orthopedist, ophthalmologist, or other specialist according to the nature of the basic handicap. It is the stressing of this attitude that makes Kanof's discussion of a rehabilitation unit of interest.

"THE JOURNAL OF TROPICAL PEDIATRICS"

IN JUNE the first number of a new pediatric journal devoted "to all problems of Child Health in Subtropical and Tropical Countries of the World" made its bow. It will be published quarterly under the editorship of Dr. D. B. Jelliffe of the All-India Institute of Hygiene and Public Health in Calcutta. The members of the Editorial Board represent a number of countries, including India, Siam, Australia, Uganda, Egypt, Indonesia, and the Philippines. The first issue contained seven articles, including "The organisation of child health services in developing countries" by Williams of the London School of Tropical Medicine; "The danger period during weaning" by Welbourn of Uganda; and "Clinical observation on kwashiorkor in Calcutta" by Mukherjee and Jelliffe of Calcutta. The journal is in English and is published in London.